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ORIGINAL ARTICLES

TETRALOGY OF FALLOT: ESPECIALLY THE CARE OF THE CYANOTIC INFANT AND CHILD

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THE operation developed by Dr. Alfred Blalock for pulmonary stenosis and atresia has definitely proven that a child with tetralogy of Fallot can be greatly benefited by increasing the circulation of blood to the lungs. Such an operation causes a prompt rise in the oxygen saturation of the arterial blood and an immediate improvement in the patient's color. If the patient has suffered from attacks of paroxysmal dyspnea or loss of consciousness, such difficulties are immediately overcome. Although the heart is not normal, the red blood cell count, the concentration of the available hemoglobin and the hematocrit reading gradually return to normal values; the clubbing of the extremities recedes and there is a great increase in the exercise tolerance of these individuals.

In childhood, the diagnosis of a tetralogy of Fallot is relatively easy. Cyanosis usually dates from birth or early infancy. The child generally develops the habit of squatting as soon as he begins to walk. Although the explanation of this is not clear, almost all children who suffer from a reduction of the pulmonary blood flow get relief by squatting.

On physical examination there is cyanosis of varying intensity and usually clubbing of the fingers and toes. The heart is but slightly if at all enlarged; generally there is a systolic murmur and thrill along the left sternal border and a clear second sound; the pulse pressure is narrow. The red blood cell count, the amount of available hemoglobin and hematocrit reading are increased. The electrocardiogram shows a right axis deviation and the teleoroentgenogram reveals a concave curve at the base of the heart to the left of the sternum. Fluoroscopy is of prime importance because absence of pulsations in the hila of the lungs is a prerequisite for operation.

Childhood is the ideal time for operation. Children between five and nine years of age have a 90% chance of being greatly improved by operation and at least as good a chance of maintaining the improvement.* Therefore the indications for operation depend

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* Follow-up studies to be reported by Whittemore and Taussig.

solely upon the incapacity of the individual and the extent of the polycythemia. If the child can walk only a few feet or even half a block, operation is clearly indicated. A child who can walk only three or four blocks before operation, may be greatly benefited by operation. Occasionally prior to operation an older individual with well developed collateral circulation may be able to walk half a mile or even miles provided he walks slowly. If, however, such a patient has a red blood cell count of 8.5 or 10 million, the polycythemia predisposes to cerebral thrombosis. Operation will cause a prompt fall in the red blood cell count, in the level of the hemoglobin and the hematocrit reading, and eliminate this danger. For this reason operation is indicated.

Infants present a far more difficult problem. The youngest successful operation has been on a five months old infant. The operative risk is more nearly 30% than 10%; moreover, the long time results have not been as satisfactory.

All of these factors render it desirable whenever possible to postpone operation until childhood. The purpose of this paper is to discuss the medical care of the cyanotic infant and the ways and means of aiding an infant to survive until he is old enough to withstand operation.

It is important to appreciate that many malformations which ultimately lead to persistent cyanosis, may not cause cyanosis at birth. Failure to gain weight is often the initial complaint. If, however, the failure to gain is related to a malformation of the heart, physical examination will reveal evidence of some cardiac abnormality. Some of these infants present extremely difficult feeding problems. They have difficulty in the digestion of food. Small and frequent feedings are often helpful. Cereals and vegetables in small amounts may be better tolerated than a large amount of milk. Weight gain is often extremely slow. Indeed a normal weight gain is a favorable sign.

During the first months of life a tetralogy of Fallot may be indistinguishable from a ventricular septal defect. In both malformations the heart is of normal size and there is only a harsh systolic murmur. The absence of cyanosis in the tetralogy of Fallot is due to the patency of the ductus arteriosus. So long as the ductus remain patent, the combined blood flow through it and the stenosed pulmonary artery may direct sufficient blood to the lungs so that cyanosis is not apparent. Delayed closure of the ductus is common in these infants. Therefore it is frequently not until three to six months of age, sometimes even after that, that cyanosis becomes apparent. Not infrequently the baby suddenly has an "attack" of cyanosis. These attacks may become progressively more numerous; cyanosis increases in intensity and finally it becomes persistent. Cyanosis, in itself, is not an indication for operation, nor is it necessarily an indication for the administration of oxygen. In many instances although cyanotic, the infant will be quite comfortable without supplementary oxygen.

Attacks of severe paroxysmal dyspnea are common in infants who suffer from anoxemia. The attacks may be precipitated by nursing, crying or by a bowel movement or they may occur without any apparent cause. The infant gives a sharp cry, becomes intensely cyanotic and gasps for breath. The attack may progress to loss of consciousness. Occasionally an infant may die in an attack. Usually, however, the attack wears off and the color improves. Indeed most infants survive many attacks. The treatment of such attacks is to turn the infant on his abdomen and place him in a knee-chest position. If this does not give immediate relief, morphine is the drug of choice: the dose is 1.0 mg./5 kg. body weight. Although morphine usually is not given to patients in respiratory distress, it is almost specific for the relief of paroxysmal dyspnea due to in-

adequate pulmonary blood flow. Not only does the dyspnea become less but the color improves. The beneficial effect of morphine in older children is dramatic. A child who is deeply cyanotic and gasping for breath and may even need artificial respiration will in half an hour have good color and be up and running around the clinic and be entirely comfortable for the next four hours. Although a child can not live on morphine, it may be life saving. If an infant is not seen until the attacks of paroxysmal dyspnea are diminishing in number or severity, for example one attack every two or three days instead of three or four attacks daily, it is usually possible to postpone operation until childhood. The early development of attacks of paroxysmal dyspnea is an unfavorable sign. The period of greatest difficulty occurs while the ductus arteriosus is undergoing obliteration. In an infant with a venous-arterial shunt this usually occurs between 6 and 18 months of age. As the patient begins to develop collateral circulation and compensatory polycythemia, the attacks of paroxysmal dyspnea diminish. Most infants who survive until 18 months of age will hold their own until two years of age and then begin to improve.

Many infants with a severe malformation of the heart and a venous-arterial shunt have a normal red blood cell count and show little or no cyanosis at rest. Although cyanosis is minimal, these infants may have an extremely low oxygen saturation of the arterial blood. Many an infant who appears to be in good condition will have an arterial oxygen saturation of approximately 30%. Oxygen saturations in this range are so frequently encountered in infancy as to suggest the existence of some, at present unknown, compensatory mechanism. Indeed, if the clinical condition is satisfactory and the patient is gaining weight, an arterial oxygen saturation of 30% is not an indication for operation in infancy. Twenty per cent saturation is cause for concern; below 20% is usually an indication for early operation.

If facilities are not available for the determination of the arterial oxygen saturation, a rough estimation of the available oxygenated blood can be obtained by the height of the hemoglobin level. Cyanosis is dependent on an absolute amount of reduced hemoglobin in the circulating blood. Consequently the intensity of the cyanosis varies not only with the percentage of oxygen unsaturation of the arterial blood but also with the total amount of available hemoglobin. It is well known that it takes 5 gm. reduced hemoglobin per 100 cc. circulating blood to give visible cyanosis. Consequently with a normal hemoglobin value of 15 gm./100 cc. it will require one-third of the blood to be in the reduced state for cyanosis to be apparent; whereas, if the hemoglobin value is 20 gm./100 cc. it will require but one fourth of the blood to be unoxygenated. Similarly, if the hemoglobin level is but 10 gm./100 cc. one-half of the blood must be in the reduced state to reach the threshold of "visible" cyanosis. If the child is obviously cyanotic there will be more nearly 6 gm. than 5 gm. reduced hemoglobin per 100 cc. circulating blood. This fact is important to bear in mind in the estimation of the severity of an anemia and the degree of anoxemia.

It is a common error to think that a baby with a red blood cell count of 4,000,000/cmm. and a hemoglobin value of 10 gm. does not have a severe anemia. If there is cyanosis due to a venous-arterial shunt, an infant with 10 gm. hemoglobin per 100 cc. has only 5 gm. of hemoglobin in terms of available oxygenated blood. The oxygen saturation of the arterial blood is generally far below 50% and the anemia, in terms of available oxygenated blood, is correspondingly more severe. Infants with persistent cyanosis and a moderately low red blood cell count can be helped by repeated small transfusions. It

is, however, important to explain to the parents that the transfusion will make the infant appear more cyanotic but it will also make him stronger.

Usually between one and three years of age the patient develops a compensatory polycythemia. During this period his general condition improves. Nevertheless, the increased viscosity of the blood increases the danger of thrombosis. Although cerebral thromboses have been known to occur in infants with a normal red blood cell count and severe anoxemia, polycythemia greatly increases this risk. Such episodes may be precipitated by dehydration. For this reason an adequate fluid intake should be maintained at all times especially during illnesses and in hot weather. Infants should receive 800 to 1000 cc. of fluid per day; children 1500-2000 cc. and adults 2500-4000 cc. daily. The proper regulation of fluid is especially important when a patient is hospitalized for study. If breakfast is to be omitted in the morning, either water should be given in place of breakfast or fluids must be forced during the night; if not, the patient must be given intravenous fluid. No patient with a polycythemia should ever be more than 12 hours without fluid.

Convulsion or severe headaches are frequently signs of impending thrombosis. If the patient complains of severe headache it is important to force fluids. The occurrence of a convulsion is usually an indication for oxygen, venesection and the replacement of blood by plasma, saline or a 5% glucose solution.*

The development of paresis or a hemiplegia calls for the prompt institution of appropriate therapy. Venesection and the replacement of blood by saline or glucose solution is strongly indicated. During this procedure, the patient should receive supplementary oxygen to compensate for the reduction in the number of the red blood cells. After venesection, a high fluid intake must be maintained; therefore, it is usually advisable to institute a continuous intravenous infusion of 5% glucose solution or physiologic saline.

Heparin may be of great value in the prevention of thrombosis. The objective is to prolong the clotting time approximately to 20 minutes. The initial dose is 0.5 mg./kg. body weight. Approximately the same amount of heparin per hour is required to maintain the clotting time at a given level as is required to raise it to that level. This amount is best given by adding heparin to a flask of glucose or saline solution which is administered by a continuous intravenous drip. It is usually advisable to continue heparin therapy for 12 hours and sometimes for 24 hours. If there is no improvement after 48 hours, little can be expected from its continuation. The administration of heparin does require repeated checking of the clotting time. With prompt institution of therapy, in most instances, residual hemiplegia can be prevented. Furthermore the extent of improvement after operation is remarkable. Therefore the occurrence of a hemiplegia is usually an indication for operation.

In general, however, most cyanotic infants do better than the doctor expects. They survive colds and infections remarkably well. If they die it is usually from anoxemia; not from intercurrent infections. It is the rare exception for an infant to die in his first attack of paroxysmal dypnea; most survive many attacks. If the number of attacks per day is lessening, or if the attacks can be relieved by the knee-chest position, and if the

* Fifty per cent glucose solution is contraindicated and 10% glucose solution should be used with caution.

infant is gaining slowly, there is less risk in the postponement of operation than in early operation. On the other hand, if the attacks are so long and severe that death is im-

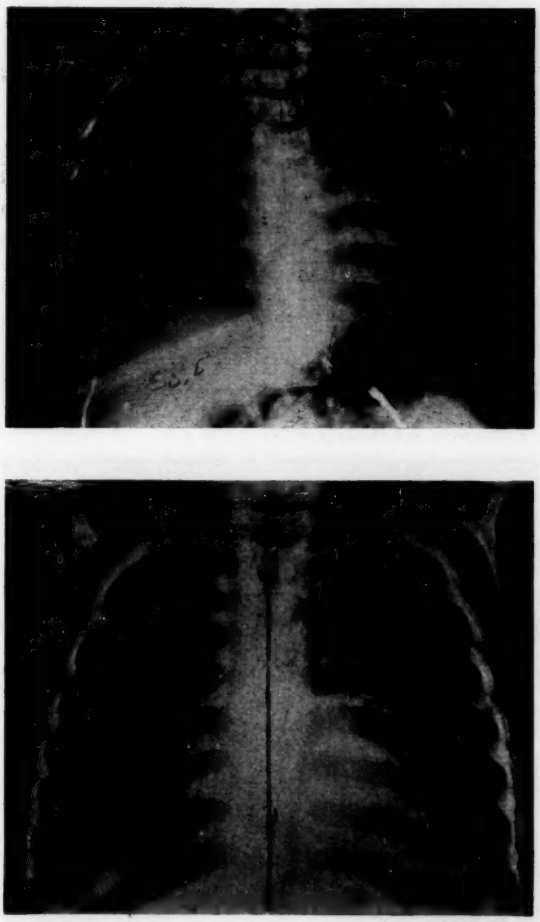

FIG. 1 (Case 1). Tetralogy of Fallot with right aortic arch, 7 months and 18 months after anastomosis of innominate artery to right pulmonary artery.

minent, even though the operative risk is high and the long time results doubtful, operation is indicated for it offers the possibility of great improvement.

The two case reports following are excellent examples.

Case 1. M.G.B. (HLH A 45754) was seen first at five months of age because of persistent cyanosis and severe paroxysmal dyspnea. The patient was blue at birth and always remained so. She had her first attack of paroxysmal dyspnea at two weeks of age. At two months she had three severe attacks in one day and thereafter continued to have repeated severe attacks.

Physical examination: T 37° C., P 140, R 36, Wt. 5.5 kg. The heart was slightly enlarged. There was no thrill and only a questionable systolic murmur. The lungs contained numerous rales. The liver edge extended two finger breadths below the costal margin; the spleen was not felt. There

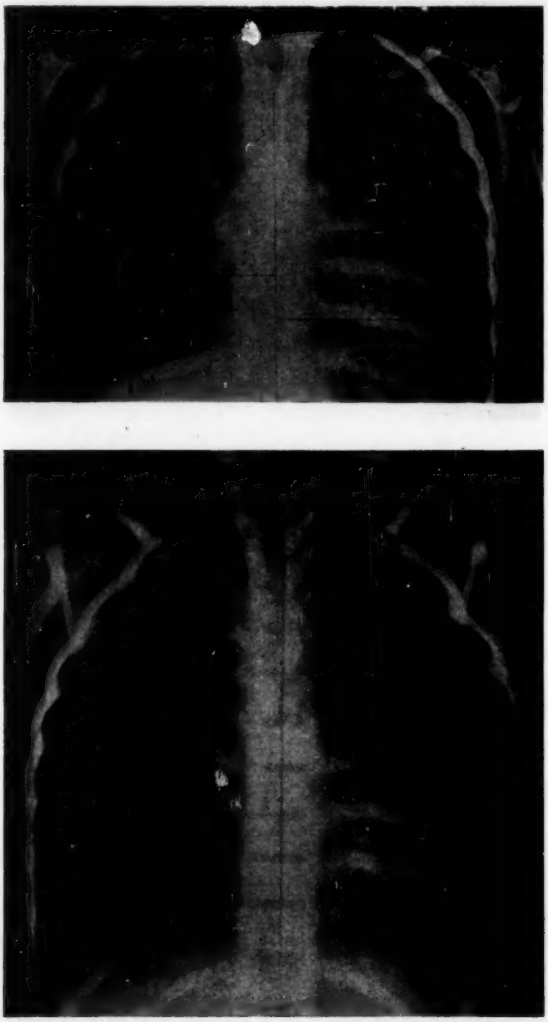

FIG. 2 (Case 2). Tetralogy of Fallot with right aortic arch, three weeks and two years after anastomosis of the innominate artery to the right pulmonary artery.

was a good pulse in the femoral artery. The fingers and toes showed marked cyanosis and early clubbing. Fluoroscopy revealed a heart of normal size, no fullness of the pulmonary conus, a right aortic arch, a clear pulmonary window and clear lung fields. Electrocardiogram: right axis deviation. Laboratory data: RBC 5.5 million, Hct 55. Oxygen saturation of arterial blood: 20%.

Diagnosis: Tetralogy of Fallot and bronchitis.

She was admitted to the Harriet Lane Home and treated with penicillin, oxygen and morphine. While in the hospital she had many extremely severe attacks of paroxysmal dyspnea; therefore, as soon as she had recovered from her respiratory infection, she was submitted to operation. The innominate artery was anastomosed to the right pulmonary artery. The infant was greatly improved. Three weeks after operation: oxygen saturation of arterial blood 69%, RBC 4.9 million and Hct 44. Nine months after operation: oxygen saturation 80% (crying vigorously), RBC 5.7 million, Hct 43, Hgb 14 gm. She has grown and developed normally. One and a half years after operation: RBC 5.25 million, Hct 44.8, Hgb 14.2 gm. The heart enlarged slightly in the immediate postoperative period but since then has shown no further increase in size (Fig. 1).

Case 2. C.B. (HLH A 44110) was first brought to the Harriet Lane Home at two years of age because of severe attacks of paroxysmal dyspnea. A heart murmur had been heard at one month of age. At five months of age she had her first attack of paroxysmal dyspnea. Thereafter she had three to five attacks per day. At the onset of these attacks she would give a sharp cry and then become cyanotic and intensely dyspneic. Over a period of months the attacks were becoming less frequent but more severe. She started to walk at 15 months. On good days she was able to walk 100 feet before squatting. After a long severe attack she was exhausted for the entire day.

Physical examination: T 37.8° C, P 100, R 30, BP 90 mm. Hg. determined by palpation and Wt. 8.5 kg. The general appearance was that of a relatively comfortable, slightly cyanotic child. The heart was not enlarged. There was a systolic thrill and a systolic murmur over the precordium. The lungs were clear. The liver edge was at the costal margin. The kidneys and spleen were not felt. There was a good pulse in the femoral artery. There was moderate cyanosis but no clubbing of the extremities. Fluoroscopy showed an absence of fullness of the pulmonary conus, a right aortic arch, an abnormally clear pulmonary window and clear lung fields. The electrocardiogram showed a right axis deviation. The clinical diagnosis was a tetralogy of Fallot with a right aortic arch.

That night the child had a severe attack of paroxysmal dyspnea. Because of these severe attacks, operation was decided upon and blood studies were postponed until her admission to the hospital could be arranged.

When she returned she was suffering from a long severe attack of paroxysmal dyspnea, so severe that death seemed imminent. Consequently an arterial puncture was not attempted until the child was anaesthetized. After a child has received morphine (which is part of the immediate preoperative medication) and is anaesthetized and is receiving oxygen, the oxygen saturation of the arterial blood is maximal. In this instance the oxygen saturation of the arterial blood was 45%, the red blood cell count was 8 million per cmm., the hematocrit reading was 85.

The innominate artery was anastomosed to the side of the left pulmonary artery; the patient made an excellent recovery. Following operation the oxygen saturation of the arterial blood rose to 82%, the red blood cell count declined to 5.7 million per cmm., the hemoglobin to 13.5 gm./100 cc. and the hematocrit reading to 43.

The heart enlarged slightly in the immediate postoperative period but has shown no further increase in size in the past year (Fig. 2) and to date she has maintained her improvement.

Summary

A patient with a tetralogy of Fallot may be greatly improved by operation. Childhood is the ideal time for operation. In infancy the mortality rate is high and the long-time results are less satisfactory. Therefore, whenever possible it is wise to postpone operation until childhood.

An infant with a tetralogy of Fallot may not be cyanotic at birth. Difficulty in feeding may be the initial complaint. Digestion is difficult; small and frequent feedings are usually indicated.

Attacks of cyanosis and paroxysmal dyspnea are prone to occur as the ductus arteriosus undergoes obliteration. Paroxysmal dyspnea is best treated by placing the child in a knee-chest position. If this does not give immediate relief, morphine should be used. A dose

of 1.0 mg./5 kg. body weight is almost specific for the relief of paroxysmal dyspnea.

Anemia is treated by blood transfusions.

Cerebral thromboses when they occur in an infant with polycythemia should be treated with oxygen, venesection and the replacement of blood by plasma, 5% glucose or saline solution. Heparin may be a great help in the prevention of residual cerebral thrombosis.

If an infant is in great danger of dying of anoxemia, surgery holds the possibility of tremendous benefit. Two such cases are cited.

SPANISH ABSTRACT

Tetralogia de Fallot: Especialmente el Cuidado del Niño Cianotico

Los pacientes con Tetralogia de Fallot pueden ser muy mejorados por medio de intervenciones quirurjicas. La mediana infancia es la epoca ideal para la operacion. En el niño pequeño la mortalidad es muy elevada y ademas los resultados post-operatorios son menos satisfactorios, por consiguiente, es juicioso posponer la operacion hasta que el niño sea mayorcito.

Un niño con Tetralogia de Fallot puede no ser cianotico en el momento del nacimiento. Dificultades en la alimentacion pueden ser los trastornos iniciales. Generalmente trastornos digestivos. Pequeñas y frecuentes comidas son generalmente indicadas en esos casos.

Crisis de cianosis y disnea paroxistica suelen ocurrir en la obliteracion del conducto arterioso. La disnea paroxistica aconseja colocar el niño en una posicion sentado hacia adelante, con el pecho sobre las rodillas; si esa actitud no mejora la crisis inmediatamente se requerira el uso de la morfina, a la dosis de 1 decimo de mlgs. por cada 5 kilos de peso, lo cual resulta casi especifico en el tratamiento de la disnea paroxistica.

La anemia es tratada con transfusion sanguinea.

La trombosis cerebral ocurrida en los niños con policitemia sera tratada con oxigeno, sangria y restitucion del volumen sanguineo con plasma y solucion glucosada al 5% o solucion salina. La heparina puede ser de gran utilidad en la prevencion de la trombosis cerebral.

Si un niño corre el riesgo de morir anoxenico el tratamiento quirurjico puede resultarle altamente beneficioso. Dos observaciones de estos casos son citadas.

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CONGENITAL ENCEPHALO-OPHTHALMIC DYSPLASIA

Epidemiologic Implications

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INTRODUCTION

EPIDEMIOLOGIC and clinical evidence indicates that congenital encephalo-ophthalmic dysplasia results from systemic insult to the fetus during or shortly after the second trimester of gestation. This report presents three new cases, summarizes previous studies, and, utilizing epidemiologic methods previously applied to mongolism,[1] interprets available data. Mongoloid defects originate earlier in gestation and differ morphologically; but both syndromes appear to be manifestations of similar biologic phenomena.

NATURE AND PATHOLOGY OF THE SYNDROME

Variants of ocular lesions which include a persistent hyaloid artery have been recognized since 1873[2] but Terry[3] first drew attention (1942) to retrolental fibroplasia as a group phenomenon related to prematurity. Ophthalmoscopic examination of six prematurely born babies when about six months of age revealed characteristic connective tissue formation in the residual meshwork of the hyaloid artery behind the crystalline lens. The lenses of one showed a normal red reflex at the age of eight weeks, but retrolental opacity at the age of six months.

Reese and Payne[4] subsequently demonstrated variable pathologic changes depending on the extent of associated hemorrhages and the presence or absence of scar tissue, contractures, glaucoma and the like. An association with hemangiomatous lesions of the skin, face, scalp, body or extremities occurred in seven of fifty cases.

The observations of Krause[5] brought appreciation that the ocular lesions were only part of a group of frequently associated anomalies that involved the central nervous system as well as the eye and the skin (hemangiomas). Five of eighteen patients had hydrocephalus. Autopsy of six patients revealed heterotopias, hyperplasia, hypoplasia or dysplasia of the cerebrum and the cerebellum. Krause in urging further study of the disease as a pathologic entity remarked that "Various aspects have been presented—the ocular disease by the ophthalmologists, the cerebral dysplasia and hydrocephalus by the neurologists and the blindness and mental retardation by psychologists and psychiatrists."

The etiology of the syndrome remains problematic and no one factor has been consistently associated with its production. Prematurity has been stressed by Terry[6] as a predisposing factor and precocious exposure to light as the most tenable cause. Reese and Payne were "inclined to believe that the same factor which precipitates early birth may also cause the eye lesions." Reviewing 18 cases, Krause found no evidence that the disease was of genetic origin. He concluded "it is possible . . . that there is a relationship to a nongenetic constitutional defect. A comparable disease is mongolism."

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Case Reports

Case 1. A boy, age three months, was found on ophthalmoscopic examination to have bilateral retrolental fibrosis.

The father, mother and one sibling were in good health. The mother was 31 years old and had had no miscarriages. At 6, 6½ and 7 months of gestation she had episodes of bright bleeding requiring hospitalization. At 7½ months spontaneous rupture of the membranes occurred and cesarean section was performed under gas-oxygen anesthesia and with no unusual amount of bleeding. An almost complete placenta previa was found in the lower uterine segment.

The baby weighed 1.6 kg., was delivered in apparently good condition and immediately placed in a Hess bed, given continuous oxygen and allowed to go 60 hours without feeding. Gavage feedings were then started. Because of persistent muscular tenseness and generally unsatisfactory progress, a lumbar puncture was performed at the end of the first week of life. The case record stated that the spinal fluid was "prune juice colored material which was obviously the result of an old intracranial hemorrhage. It was felt that there had been some anoxemia at the time of the maternal bleeding three weeks before delivery which resulted in central nervous system hemorrhage at that time." The baby gained weight and appeared to do well except for an anemia of 3 million RBC with 7.6 gm. Hgb./100 cc. blood which persisted for over a month despite liver extract and ferrous sulfate (elixir feosol). Nothing abnormal about the eyes was noted in the neonatal period.

At the age of three months the baby was noted to have opacities of both eyes. Ophthalmoscopic examination revealed a "fibrovascular sheath of the lens. It is very dense and filled with vessels so that one can get no red reflex from the fundi. The pupils do not seem to react to light, although after shining the light on them a little while they did seem to be a little smaller."

By the age of four months, hemoglobin had risen to 12.5 gm. The baby was alert and the general condition excellent except for blindness. However, he had begun to vomit and this continued persistently and with increasing frequency. At the age of five and one-half months he developed a respiratory infection and bulging fontanelle. He was, therefore, admitted to a hospital for treatment and investigative procedures.

A roentgenogram of the chest was negative. White blood cell count was not elevated. Ventricular tap yielded straw-colored fluid containing much protein. Ventriculograms showed all the ventricles moderately dilated and considerable air over the cerebral hemispheres. The baby improved and was discharged after nine days, but the subsequent course was characterized by progressive cachexia, increasing hydrocephalus, and death within a few weeks.

Necropsy examination demonstrated a small, flat, reddish papule of the skin 1 cm. in diameter, to the left of the umbilicus. Diffuse bilateral cerebral cortical deficiency was associated with marked dilatation of the lateral ventricles. The meninges were thickened by great numbers of disorganized strands of coarse fibers which stained intense pink with eosin giving the appearance of collagen, while with the phosphotungstic acid stain these fibers were dark blue. With them were elongated pale cells which resembled fibroblasts in appearance. The bulk of the meningeal thickening was due to an abundance of fine reticulum, frequently merging imperceptibly into brain tissue though more often clearly demarcated.

A large gelatinous mass covered the upper medulla, pons and surrounding portions of the cerebellum, and extended widely over the base of the brain. In many areas it was separable from underlying brain by blunt dissection revealing a distinct line of cleavage, but in other areas it was adherent. Two large masses of muco-gelatinous substance had assumed the shape and position (though greatly enlarged) of Ammon's Horns. The foramina of Luschka and Magendie were obstructed and the foramen of Monro and the third ventricle were encroached upon. Microscopic examination showed the mass to be composed of normal brain elements, glial cells and fibers, and scattered nerve cells. The intercellular substance was composed of a fine, cobweb-like reticulum staining pale yellow with eosin and pale pinkish-yellow with phosphotungstic acid. Coursing through this tissue in a striking pattern were exceedingly numerous blood vessels, obviously abnormal in number, structure and distribution. Sparse in some areas they were grouped in others so as to form microscopic angiomata. Some were of the capillary type and consisted of a regular layer of flattened endothelial cells lined by a thin, collagenous membrane. Others displayed marked thickening of the walls, which, however, was not homogenous but patchy in distribution, so that thin and thickened portions alternated. The thickening was due to a proliferation of connective tissue fibers which showed a tendency to fuse together in blocks of sclerotic, hyalinized material. Collagenous fibers

departed at times from the vessel walls in cobweb like fashion to interlace with the network of fibers of the surrounding tissue.

The impression was of an hamartomatous process in the composition of which the blood vessels had taken an outstanding part.

Case 2. A girl, five months of age, examined ophthalmoscopically had bilateral retrolental fibrosis with loss of the red reflex.

The father, mother (age 31) and two siblings were living, one sibling having had nephrosis. In the sixth month of gestation the mother was in a hospital for three days with an upper respiratory infection, rhinitis and sinusitis. Laboratory studies revealed a moderate leukocytosis of 17,900 WBC, 4.2 million RBC and 12.6 gm. Hgb./100 cc. blood. Low abdominal cramp-like pains were experienced the day after her return home and brownish vaginal bleeding was noted. The patient returned to the hospital for two and one-half weeks. Intermittent bleeding continued and ultimately fresh bleeding of an intensity necessitating cesarean section. The red blood count had fallen to 3.8 million cells and the hemoglobin to 11.7 gm. Operation under gas-oxygen-ether anesthesia showed the umbilical cord to have a villous insertion into the placenta. A note by the obstetrician read: "Cord splayed out on approaching the placenta and apparently one of the cord veins had ruptured which accounted for the bleeding."

The baby weighed 1000 gm., cried well and was apparently normal. She was placed in a Hess bed and given continuous oxygen. With gavage feedings of a 2% milk formula supplemented with vitamins she gained steadily to 2300 gm., at the age of two months. Thereafter the gain was slower and an anemia of 3.6 million RBC with a 6.0 gm. Hgb. was determined at the age of four months. Following administration of ferrous sulfate (elixir feosol) for a month the hemoglobin rose to 8.1 gm. Apart from the gross visual defect occasioned by the retrolental fibroplasia manifest at five months, her progress through infancy was generally uneventful. At one year of age the weight was about 7 kg.; at two years 10 kg.

Although development was retarded at two years of age, accelerated progress was made between two and four. After the age of four vision improved so that despite a searching nystagmus she was able to play around with other children in nursery school, at which stage mental and physical development were reported within normal limits.

Case 3. A boy 7½ months of age was found by ophthalmoscopic examination to have retrolental fibroplasia of the left eye.

The mother was 27 years old at the time of pregnancy and had two healthy children. Her health was good as far as known and she had experienced no miscarriages. Pregnancy was uncomplicated except for episodes of bright bleeding from the vagina in the fourth and fifth months, each requiring hospitalization for approximately a week. The cause of the placental bleeding was not determined although placenta previa was eliminated as a factor. Seepage of amniotic fluid occurred for more than a month before spontaneous delivery ten weeks before the anticipated date. Birth weight was 1200 gm. No postnatal disturbances were noted.

Multiple hemangiomas, about eight in all, were present over the right scapular area, scalp, trunk and extremities, varying from about two inches to less than a quarter of an inch in diameter. Periodic ophthalmoscopic examinations revealed no abnormalities until age 7½ months, when a pinkish gray band of tissue was seen to extend from the disc of the left eye horizontally to the back of the lens on the temporal side. A remnant of the hyaloid artery projected into the vitreous but was not attached to the lens. The right eye appeared normal. The weight curve throughout the first year and a half showed normal increments, but the motor and mental progress was retarded.

At 14 months a small whitish area containing some dark pigmentation was observed at the extreme temporal periphery of the fundus of the right eye. By 20 months of age a fine, small retrolental membrane had developed in the upper, outer quadrant of the right eye. A separation of the retina had occurred beneath the macula of the left eye.

Epidemiology

Clinical knowledge of encephalo-ophthalmic dysplasia has been greatly extended by the studies of Terry, Reese and Payne, and Krause, but the diverse clinical pattern in individual cases is still obscure.

It becomes increasingly evident that the technics of the epidemiologic method frequently contribute to the explanation of such divergencies through study of the mass pathology of disease; and that the study of groups complements and often extends the results of detailed observations on the individual. To this end, the data reported here and those collected by Terry, Reese and Payne, and Krause are brought together for epidemiologic analyses.

Prevalence Among Prematurely Born Babies:

The ratio of encephalo-ophthalmic dysplasia to total births in the Chicago Lying-in Hospital (time not stated) was 1 to 4,000.[5] The association with prematurity observed by Terry has been confirmed.[4, 5] Infants were premature judged by a birth weight of less than 2300 gm., in 51 (about two-thirds) of 76 cases. They weighed less than 1350 gm. in 14 (about one-half) of the 26 cases where the specific figure was given.

Sex Ratio and Ratio of Multiple Births:

In this series there was a slight preponderance of males (43 of 76 affected babies)—not significant for the numbers observed. Ten of the 76 mothers gave birth to multiple offspring—8 pairs of twins (normal expectancy for 750 births)[7] and two sets of triplets (ordinarily expected in 20,000 births).[7]

Age When Ocular Abnormality Was First Observed in Relation to Prematurity:

A congenital origin is established when ocular disease is observed at birth or in the immediate neonatal period. First appearance of the lesion some months after birth has

TABLE I

AGE AT WHICH ABNORMALITY WAS RECOGNIZED IN RELATION TO PREMATURITY*

	Age at which abnormality was recognized		
	Less than one month	Within 1–3 months	After 3 months
Prematurely born infants	2	6	18
Infants born at term	13	2	1

* Birth weight under 2.3 kg.

been interpreted as eliminating the possibility of natal or prenatal origin. That another interpretation is possible is indicated by evidence that the congenital disease is generally limited to a particular group—infants born at term (Table I).

The ratio of premature to term births (2:13) when the condition was recognized during the first month of life shows a complete reversal (18:1) after the third month. The differences may find explanation by Terry's finding—that the pathologic process is a progressive one. He observed the retrolental membrane to develop gradually behind previously clear lenses in three patients during the first six months of postnatal life. Each infant was markedly premature.[3, 8] A similar instance has been observed in Case 3. If several months are required for the retrolental membrane to manifest itself, then the low incidence of ocular lesions in premature infants and the high incidence

among full-term infants suggests that the causative agent acts generally at about the time the premature group was born, and therefore well before birth of the term group.

Relation to Maternal Age:

Ages are recorded of 25 mothers of babies with encephalo-ophthalmic dysplasia. These are compared in Figure 1 with the ages of more than two million mothers of the United States Registration Area in 1944.[7] More data are needed before the trend can be definitively characterized, and before it can be determined whether or not a relation may exist between disease in the child and the mother's age.

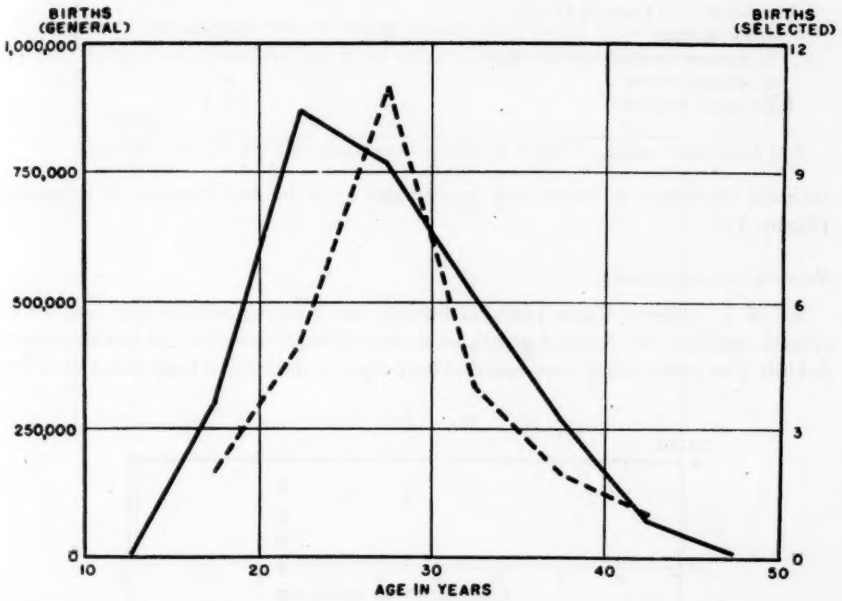

FIG. 1. Maternal age of two million mothers in the United States Registration Area in 1944;[7] and 25 mothers of babies with encephalo-ophthalmic dysplasia.

Relation to Maternal Health during Pregnancy:

The facts indicating an association between encephalo-ophthalmic dysplasia and prematurity also point to a possible relation to the kind of pregnancy which results in premature birth. A compilation of available data is summarized in Table II. Twenty-one (28%) of 76 mothers had placental disease identified as such, or manifested by gross gestational hemorrhage or prolonged seepage of amniotic fluid. The nature of the placental disease was identified twice as placenta previa, once as rupture of a vessel at the site of villous insertion of the umbilical cord, and once as due to an anomalous amnion. Ten (13%) of the group had multiple births; 8 (10%) had intercurrent infections, and 3 (4%) toxemia of pregnancy. The significance of such findings, suggested by observed frequencies as compared with ordinary expectancies (Table II), is demonstrated by the groupings of deliveries at a particular stage of gestation (Figure 2); and of the occasional

TABLE II

ENCEPHALO-OPHTHALMIC DYSPLASIA AND MATERNAL HEALTH—76 MOTHERS

Maternal health	Cases Observed	Rates per 1,000 pregnancies	
		Observed	Expected[7,9,10]
Premature Labor*	51	671.0	31.2
Toxemia of Pregnancy	3	39.6	2.0
Multiple Births—Twins	8	105.3	10.6
Triplets	2	36.3	0.1
Manifestation of Placental Disease:			
1. Hemorrhage	18	236.8	
2. Prolonged seepage amniotic fluid	3	39.5	
3. Placenta Previa	2	26.3	5.5
Intercurrent Infections	8	105.3	

* At 8 months or earlier, or judged by delivery of an infant weighing less than 2300 gm.

antenatal respiratory infections and hemorrhages after the first trimester of pregnancy (Figure 3).*

Relation to Infant Health:

Six of 27 patients whose postnatal histories are recorded had definite cyanosis or cyanotic attacks in the neonatal period, or absence of respirations for at least two minutes at birth. Five subsequently were found to have signs of intracranial hemorrhage of whom

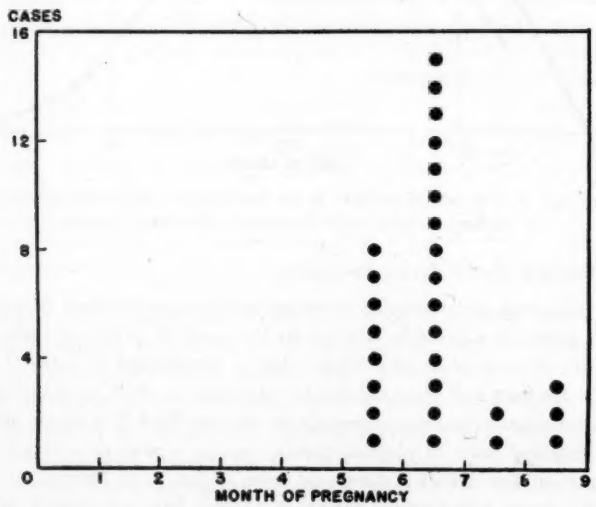

FIG. 2. Distribution of 28 cases of encephalo-ophthalmic dysplasia by periods of gestation.

* Information necessary to date the event is provided by Terry's cases 1, 2, 3; Krause's cases 11, 12; and 3 cases reported here.

three developed hydrocephalus. Two other babies born at term had congenital hydrocephalus. Two other infants subsequently became spastic, making a total of seven patients with encephalo-ophthalmic dysplasia who also had hydrocephalus, intracranial hemorrhage or spasticity. The significance of the association with hydrocephalus is demonstrated by the fact that 4 of the 76 infants died of the condition under one year of age. General expectancy is less than 1 per 1,000 live births.[7] Though the significance of other findings is questionable, taken all together they suggest that anoxia may play a major role in the pathogenesis of subsequently developing disease.

Relation to Multiple Birth:

If a series of infants with twin or triplet siblings is grouped by a common criterion, then the siblings form a second group of epidemiologic interest. Of all groups in the

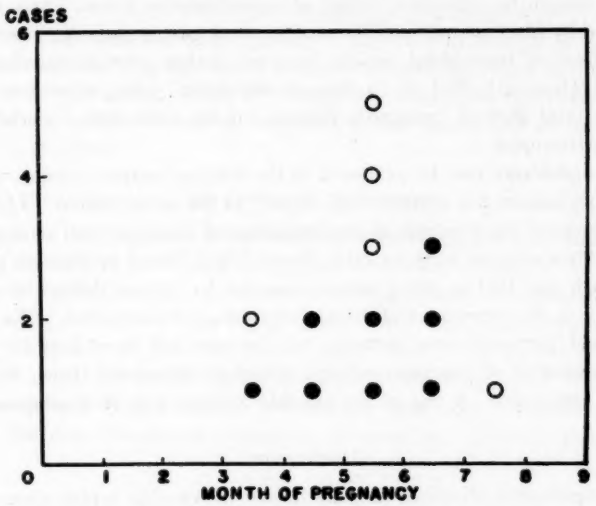

FIG. 3. Intercurrent infection (○), 4 mothers; and antenatal hemorrhage (●), 5 mothers, by month of pregnancy.

general population the second is most likely to have partaken of the same hereditary components and the same post-conceptual influences as the first.

The eight instances of multiple pregnancy contributing eight individuals to this series resulted in the premature birth of these eight babies, in addition to which there were ten siblings. Six of the ten died in the neonatal period and one other at the age of four months with the status of the eyes unspecified. Two of the three surviving siblings are recorded to have developed ocular anomalies. A high neonatal mortality (66% in this small group) was observed among twin or triplet siblings of an individual afflicted with encephalo-ophthalmic dysplasia and a disposition of the survivors to develop the condition.

The reasonable inference is to be drawn that all individuals concerned were subjected to sublethal action of an agent before or during the time of delivery; with the slight

margin between death and injury, or injury and escape determined by minor differences in host, placental environment or agent. In five of the eight sets of twins and triplets at least one baby had significant degrees of cyanosis, atelectasis, intracranial hemorrhage, or suffered from the effects of placental abnormalities (amniotic band formation).

Because of the absence of pathologic evidence of infectious agents; because of the relationship to prematurity in this whole group of multiple births; because of the character and great variability of clinical manifestations; and because of similar findings among the large group of premature infants born singly, it is inferred that the active agent was often sublethal anoxia.

Relation to Angiomata and Their Dissociated Growths:

Twelve of 77 patients had either single or multiple hemangiomas of the skin. One patient (Case 1) had in addition massive infiltration of the subarachnoid space and cerebrospinal system by gelatinous masses of hamartomatous tissue. These tumors have been identified by MacCallum,[11] and Karsner[12] with angiomata arising "from a rudiment which is destined to form blood vessels, from which they grow independently."[11] One other patient (Krause[5]) died of "a mass in the brain" later referred to as a brain tumor, and a third showed "gelatinous substance in the cerebellum," arachnoidal thickenings and heterotopias.

The same significance may be attributed to the hemangiomatous lesions of encephalo-ophthalmic dysplasia as was attributed by Mann[13] to the ocular lesions. "These cases are all good examples of the principle of the production of developmental anomalies through arrest at a definite stage of intra- or extra-uterine life followed by aberrant growth. This aberrant growth may lead to excess normal tissue or, by atypical differentiation of pluripotential cells, to the appearance of tissue abnormal in that situation." The presence of heterotopic and hamartomatous elements may be similarly viewed as the product of atypical differentiation of pluripotential cells forming a dissociated tissue. Mall[14] demonstrated that "dissociation" is one of the possible consequences of developmental arrest* (1908).

Discussion

Encephalo-ophthalmic dysplasia is characterized by variable ocular anomalies including retrolental fibroplasia; by commonly accompanying structural and dissociated malformations of the cerebrum; and often by single or multiple hemangiomas of the skin. Particular manifestations and groupings are no more uniform than they are for the congenital cataracts, cardiac anomalies and cerebral defects which have been demonstrated to arise as developmental arrests following rubella in the first trimester of pregnancy (Gregg and Swan.)[16, 17] The nature of the deformity is related to the stage of gestation in which rubella occurs and rather assuredly to variations of host, agent, and placental environment (Ingalls and Gordon[18, 19]).

Mann[13] has advanced the hypothesis that the primary cause of retrolental fibroplasia is a maternal upset probably nonspecific in nature but specific in time. The observations

* Mall's most significant discovery in connection with pathologic embryos was summed up in the term "dissociation." He meant that, since during development, the relative growth of different tissues and organs is under the control of hormones, the most striking effect of pathologic conditions on early embryos is a release from this control, making the tissues grow independently of each other exactly as they do in tissue culture (Sabin).[15]

which have been assembled here tend to verify Mann's postulate—provided adverse circumstances leading to or associated with premature birth are included in the category of "maternal upsets." This is not to imply that the adverse situation is exclusively maternal for the increased vulnerability of the markedly premature fetus to both trauma and anoxemia has been repeatedly demonstrated (Clifford[10] and Cole[20]).

Time of Origin of Ocular Anomalies:

Epidemiologic data mutually support embryologic data to indicate that the ocular anomalies of encephalo-ophthalmic dysplasia are developmental defects consequent to a maternal disturbance after the first trimester of pregnancy, with their origin for the most part at about the sixth or seventh month of gestation. These data (Table II, Figs. 2, 3) are the demonstrable relationships of the condition to maternal systemic and placental disturbances, and to premature delivery at the approximate time when the primary vitreous completes differentiation and the sheath undergoes involution. The process of normal involution of the primary vitreous and hyaloid artery follows a pattern in which the posterior vascular sheath normally becomes obliterated during the sixth and seventh month of gestation (Terry).[21] The patent artery and capillaries are, therefore, theoretically susceptible of arrested involution at this period, and are no longer so once involution is complete.

Time of Origin of Encephalic and Cutaneous Anomalies:

Anomalies of the brain and skin accompany those of the eye with sufficient regularity to warrant the inference that they usually have a common etiology at the same period of development. An isolated instance where retrolental fibrosis was associated with cardiac anomalies of first trimester origin* does not of itself negate this hypothesis. Arrests in different trimesters could be caused by a single agent acting on two occasions or two agents each acting independently and successively. An example of the first possibility would be anoxemia during successive hemorrhages from a placenta previa; of the second, rubella in the first trimester of pregnancy, followed by a placental hemorrhage in the second.

Nature of the Basic Lesion:

Terry found the retrolental lesion to consist of connective tissue traversed by patent or obliterated blood vessels. Krause demonstrated that proliferation of the glia, mesodermal connective tissue and neuro-epithelium leading to the formation of a retrolental membrane of iridic and postlental capillaries were merely parts of protean manifestations of a more general disease process involving also the central nervous system. Because of their finding of hemangiomatous lesions of the skin in seven of their 50 cases, Reese and Payne[4] postulated a relation of the ocular lesion to hemangioma. They pointed out that the primary vitreous is for the most part derived from angioblastic mesoderm, and noted that in some areas of microscopic sections studied, the retrolental tissue showed highly vascularized areas identical with hemangiomatous tissue.

In a consideration of the essential nature of the anomalies of mongolism[22] their almost constant association with anomalies of early vascular development was interpreted to

* Pulmonary stenosis, transposition of the aorta, and a septal defect of the heart found at autopsy in a patient of Reese and Payne.

indicate that many anatomically unrelated defects had a common relationship in vascular disease. The same possibility is suggested in encephalo-ophthalmic dysplasia by the frequent presence of associated hemangiomata indicative of anomalous vascular development at those sites during some stage of fetal development. It is reasonable to infer that endothelial injury represents the basic lesion; that particular morphologic features are determined by the site and extent of the injury; and that these in turn are modified by hemorrhage, necrosis, reactive, degenerative or dissociated tissue formation.

Nature of the Causative Agent:

Evidence has been presented to show that fetal anoxia concomitant with maternal systemic, or placental disease, or the birth process itself may play a major role in the causation of vascular injury leading to encephalo-ophthalmic dysplasia. The high neonatal mortality among twin or triplet siblings of an afflicted individual was interpreted to mean that other members of those multiple pregnancies were subjected to sublethal anoxia before or during the time of delivery; and that the slight margin between death, injury, and escape, together with the sites of injury, were determined by minor differences in host, placental environment or agent. It is evident that host, agent and environmental alterations may occur during birth—differing for example among each of triplets or identical twins in respect to trauma and anoxia.

If these concepts are correct, then the presence of any one type of anomaly, e.g. retrolental fibrosis, is of more clinical than biologic significance—like the cranial stigmas of mongolism. Each anomaly is no more than a part of a larger biologic pattern of disease in the developing individual. For example, the common hemangiomas of the skin, or Lindau's disease—angiomatosis of the retina with associated angiomatous involvement of the cerebellum—are specific examples of the types of vascular anomalies which could conceivably be other parts of the larger pattern. As a result of his studies on Lindau's disease (1932) Tedeschi[23] came to the conclusion that "The disembryoblastic origin of Lindau's disease is apparent and the fact that it is not infrequently accompanied by other organic malformative processes has made some consider the possibility of a more general developmental defect."

In any event, variation in findings present among twins and triplets proves the existence of a disease pattern of which ocular disease is only a part. The nature of the clinical disorder is assuredly influenced by the site and degree of ocular and extra-ocular injury, and modified by the innate sensitivity and response—hemorrhagic, proliferative, degenerative or reactive—of rapidly differentiating tissue.

In its variable clinical manifestations and in its broad epidemiologic patterns such as its association with particular maternal disturbances acting at a particular stage of gestation, encephalo-ophthalmic dysplasia bears a resemblance to post-rubella deformities and to mongolism. When the ocular lesions first appear in postnatal life following anoxia at birth, the circumstance provides an unrivaled opportunity to ascertain more precisely the basic nature of vascular arrests and the sequence of events set in motion by a specific causative agent. Among the sequellae the phenomena of dissociation and hemangioma formation are particularly worthy of study.

Conclusions

While the causative agents of encephalo-ophthalmic dysplasia are relatively numerous, the causative mechanisms are fewer in number and operate during or shortly after the

second trimester of pregnancy. Causative agents include placental abnormalities and hemorrhages; conditions leading to or associated with premature and multiple births; and possibly certain intercurrent infections of the mother. There is no evidence of a genetic factor. Clinical, pathologic and epidemiologic evidence suggests that lack of oxygen to the fetus may be the most important causative mechanism leading to permanent damage of vascular tissues. Special features of the clinical syndrome are due to the stage of development of the host at the time the injurious agent acted. They are also dependent upon the site and extent of injury, and are modified greatly by secondary changes.

References

1. Ingalls, T. H., Etiology of mongolism, Am. J. Dis. Child. **74**:147, 1947.
2. Nettleship, E., Eye lost after extraction of cataract, Roy. Lond. Ophth. Hosp. Rep. **7**:632, 1873.
3. Terry, T. L., Fibroblastic overgrowth of persistent tunica vasculosa lentis in premature infants, Arch. Ophth. **29**:36, 1943.
4. Reese, A. B., and Payne, F., Persistence and hyperplasia of primary vitreous (tunica vasculosa lentis or retrolental fibroplasia), Am. J. Ophth. **29**:1, 1946.
5. Krause, A. C., Congenital encephalo-ophthalmic dysplasia, Arch. Ophth. **36**:387, 1946.
6. Terry, T. L., Ocular maldevelopment, J.A.M.A. **128**:582, 1945.
7. Vital Statistics of the U. S. (Department of Commerce, Bureau of the Census, 1944).
8. Terry, T. L., Persistence and hyperplasia of primary vitreous, Am. J. Ophth. **29**:20, 1946.
9. Stander, H. J., Williams' Textbook of Obstetrics, 8th edition, Appleton-Century, New York, 1941.
10. Clifford, S. H., Reduction of premature infant mortality through determination of fetal size in utero; attempt to control weight at birth according to complication of pregnancy present. J.A.M.A. **103**:1117, 1934.
11. MacCallum, W. G., Textbook of Pathology, 6th edition, W. B. Saunders Co., Philadelphia, 1936, p. 1058.
12. Karsner, H. T., Human Pathology, 4th edition, J. B. Lippincott Co., Philadelphia, 1935.
13. Mann, I., Persistence and hyperplasia of primary vitreous, Am. J. Ophth. **29**:19, 1946.
14. Mall, F. P., Study of causes underlying the origin of human monsters, J. Morphol. **19**:1, 1908.
15. Sabin, Florence R., Franklin Paine Mall, Johns Hopkins Press, Baltimore, 1934, p. 306.
16. Gregg, N. M., Congenital cataract following german measles in mother, Tr. Ophth. Soc. Australia, **3**:35, 1942.
17. Swan, C. et al., Congenital defects in infants following infectious diseases during pregnancy. M. J. Australia **2**:201, 1943.
18. Ingalls, T. H., and Gordon, J. E., Epidemiologic implications of developmental arrests. Am. J. Med. Sci. **214**:322, 1947.
19. Gordon, J. E., and Ingalls, T. H., Death, defect and disability in prenatal life, Am. J. Pub. Health **38**:66, 1948.
20. Cole, W. C., Asphyxia during delivery and immediately postpartum, J. Pediat. **19**:265, 1941.
21. Terry, T. L., Fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely; studies in development and regression of hyaloid artery and tunica vasculosa lentis, Am. J. Ophth. **25**:1409, 1942.
22. Ingalls, T. H., Pathogenesis of mongolism, Am. J. Dis. Child. **73**:279, 1947.
23. Tedeschi, C., Tumori vascolari encefalici e malattia di Lindau, Riv. sper. di freniat. **56**:497, 1932.
24. Gundersen, T., personal communication.

Spanish Abstract

Displasia Encefalo-oftalmica Congenita: Inplicaciones Epidemiologicas

Al par que los agentes causales de la displasia encefalo-oftalmica congenita son relativamente numerosos, las causas mecanicas son pocas en numero y operan durante un corto tiempo despues del segundo trimestre del embarazo. En los agentes causales se incluyen anomalias de la placenta y hemorragia, condiciones que conducen o a lo menos se asocian con el parto prematuro multiple y

posiblemente con ciertas infecciones interrecurrentes de la madre. No hay evidencia de un factor genetico. La clinica, la patologia y la epidemiologia parecen responsabilizar la falta de oxigeno del feto como el factor mecanico mas importante en la produccion de permanentes alteraciones en los tejidos vasculares. Caracteres particulares del sindrome clinico se deben al momento del desarrollo y el tiempo en que el agente traumatizante ha actuado. Existen tambien una cierta dependencia entre el sitio y la extension de la lesion, que son grandemente modificadas por cambios secundarios.

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STOKES-ADAMS SYNDROME ASSOCIATED WITH COMPLETE CONGENITAL HEART BLOCK IN INFANCY AND CHILDHOOD

By SAMUEL J. NICHAMIN, M.D.
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STOKES-ADAMS syndrome is an uncommon clinical condition in infancy or childhood. The occurrence of syncopal attacks early in life with bradycardia should suggest the diagnosis of true congenital heart block. The criteria for a diagnosis of heart block include: the presence of a slow pulse noted at an early age, absence of a history of an infection that might produce heart block, signs of other congenital heart lesions, and electrocardiographic tracings showing complete a-v dissociation. Sheridan and Parker[1] have mentioned recently that about 88 authenticated cases of congenital heart block have been reported. The frequency with which this cardiac anomaly has been reported is probably not an accurate index of its actual occurrence. However, when cerebral symptoms comprising syncopal and convulsive seizures are encountered, this condition must be considered. The relationship of these manifestations is not clear.

The incidence of the Stokes-Adams syndrome associated with congenital heart block varies in the reports of the several authors. Yater[2] mentions syncopal attacks in 5 of 30 accepted cases of congenital heart block. In Hays'[3] report of three cases of congenital heart block one had frequent attacks of the Stokes-Adams type, and presumably died in an attack of syncope. Campbell and Suzman[4] found Stokes-Adams attacks in one of their eight patients. In a group of seven cases of Stokes-Adams syndrome collected by Faessler,[5] several died between six days and three months. The attacks became much less frequent in some, and ceased entirely in others.

Although the Stokes-Adams syndrome is regarded usually as a severe manifestation of congenital heart block and an unfavorable prognostic sign, Wallgren and Winblad[6] state that such cases may still survive.

A slow ventricular beat is essential for the cerebral symptoms of the Stokes-Adams attacks. As the diastolic blood pressure falls during the prolonged interval between beats, there is a diminution of the blood supply to the cerebral centers. The anoxia might be a factor in producing the convulsive disorder.

CASE REPORT

D. B., white male child, age 19 months, was seen first because of a convulsion. Two weeks previously he had developed a mild upper respiratory infection, but had otherwise been in fairly good health until the present episode. The attack lasted 20 to 30 minutes. His body temperature was 38.4° C. Respirations were labored. He was limp and atonic. There was a dusky hue to the cheeks and lips, but no definite cyanosis. The face appeared asymmetrical. The pupils were equal and regular. There was a groove-like contraction of the lower chest walls. The pulse rate was 40/min. The deep and superficial reflexes were normal. There was no clubbing of the fingers.

During the hospital admission the respirations were somewhat labored. The pulse rate varied between 38 and 50. A short systolic murmur was heard near the apex and at times a third heart sound

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(Received for publication October 13, 1947.)

could be distinguished. No thrill was felt. There was some enlargement of the heart to the left. The blood pressure was 130 mm. Hg. Convulsive attacks did not recur.

Laboratory data: Chest X-ray revealed cardiac enlargement particularly to the left, and pulmonary congestion. The configuration of the chest was abnormal. The hilar markings were prominent due to vascular congestion. Films taken after barium was swallowed showed no unusual displacement of the esophagus. Five days later X-rays showed no significant changes.

ECG showed complete a-v heart block, auricular rate 170/min., ventricular rate 35/min. P_2 was large and peaked, suggesting a congenital defect; splintered QRS in all leads; T wave poorly formed in all leads. Ventricular extrasystoles were present. There were possible other congenital cardiac defects.

Electroencephalograms. Two EEG's obtained 10 days apart showed marked variation in the degree of rhythm of repose. There were more muscle potentials in the earlier record. The records were made

FIG. 1. Asymmetry of the face and ears and groove-like contraction of the left lower chest wall were present.

of waves at 5 cycles per second (predominantly in the occipital areas). These are both normal rhythms for this age level. The asymmetry in voltage (left side greater than right) was much more obvious in the early record. There were no seizure discharges. The record was considered unstable normal. The asymmetry and the change in pattern from test to test were the chief reasons for considering the pattern unstable.

COMMENT

The syncopal or convulsive seizures that represent the Stokes-Adams syndrome can, in infants and children, serve as a guide in the diagnosis of complete congenital heart block. In this age group the presence of a persistent pulse rate below 60-70 mm. during and after a syncopal or convulsive seizure should lead to the consideration of a possible heart block.

In this case respiratory infections occurred prior to the onset of the various Stokes-Adams attacks. On other occasions excessive physical exertion appeared to be a precipi-

tating factor. On the basis of such evidence one might assume that any extra demands upon the heart may alter the inherent hemodynamics in patients with complete heart block. With the excessive slowing of the ventricles the heart must accommodate itself to an even greater quantity of blood returning to it in diastole. Pulmonary congestion may supervene. A deficient or lessened flow of blood to the brain results in cerebral manifestations such as syncope or convulsions. Clinical and roentgen ray findings of

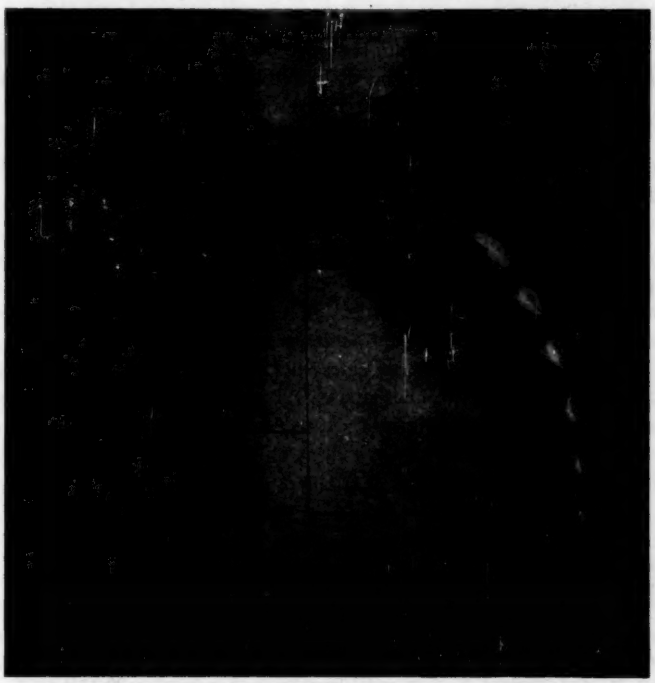

FIG. 2. Roentgenogram shows pronounced enlargement of the heart, the left border almost reaching the left lateral chest wall.

pulmonary congestion were noted in this patient whenever he was examined because of cerebral symptoms.

Yater,[2] in his report of a case of complete congenital heart block, noted an imperfect development of the face. In our patient, likewise, a definite asymmetry of the face was present, as can be noted in Fig. 1, in which the right side of the face appears fuller and more convex than the left. In addition, the ears reveal a marked asymmetry, the right being larger than the left, and with a different contour. Pulsations were more prominent on the left side of the neck. In one of the electroencephalographic tracings there was a reduction of voltage activity on the right side. The EEG was regarded as unstable normal. Tracings were not made during a syncopal or convulsive episode.

Stokes-Adams attacks must be differentiated primarily from idiopathic epilepsy. The persistent bradycardia, ECG and EEG studies readily provide the correct diagnosis.

The possibility of sudden death during a Stokes-Adams attack is an ever present danger and alters the favorable prognosis in those cases of complete congenital heart block not associated with cerebral manifestations. Evidences of cardiac failure are rarely seen in patients with congenital block.

Whether anoxia is the inciting factor for the convulsive reaction is not clear. Greenblatt[7] showed that after about 10 seconds of bilateral occlusion of the carotids an outburst of slow waves in the EEG tracing were followed almost immediately by tonic-clonic seizures of short duration. He believes this effect is due to acute interruption of the circulation to the brain. To combat the anoxia, oxygen therapy would therefore appear to be a rational procedure during the period of the Stokes-Adams attack. The administration of drugs such as atropine or digitalis seems questionable in view of the anatomic anomalies of the conduction system found at autopsy reported in congenital complete heart block. In our patient, atropine sulfate in doses as high as 0.8 mg. failed to produce any change in the pulse rate.

Summary

Complete congenital heart block with syncopal or convulsive seizure reaction (Stokes-Adams syndrome), although a rare condition, requires differentiation from other types of fainting spells and convulsive disorders of infancy and childhood. Symptoms of this syndrome, aside from the cerebral manifestations, are few.

Stokes-Adams attacks represent an emergency because of the possibility of sudden death. Congenital heart block without attacks is compatible with a normal life expectancy.

Stokes-Adams syndrome in this case seemed to be precipitated by mild respiratory infections and over-exertion. Asymmetric deviations of cervical pulsations, facial contour and EEG tracings were noted.

References

1. Sheridan, V. E., and Parker, R. L., Development of heart block in the neonatal period, Am. J. Dis. Child. **73**:199, 1947.
2. Yater, W. M., Congenital heart-block, Am. J. Dis. Child. **38**:112, 1929.
3. Hays, L., Report of 3 cases of congenital heart-block, J. Pediat. **4**:380, 1934.
4. Campbell, M., and Suzman, S. S., Congenital complete heart-block, Am. Heart J. **9**:304, 1934.
5. Faessler, B., Das Adams-Stokessche Syndrom in Säuglingsalter, Ann. paediat. **153**:327, 1939.
6. Wallgren, A., and Winblad, S., Congenital heart-block, Acta paediat. **20**:175, 1937.
7. Greenblatt, M., Rinkel, M., and Solomon, H. C., Studies of carotid sinus in man, Personal communication.

Spanish Abstract

El sindrome de Stokes-Adams se asocia en determinado numero de casos con el bloqueo congenito (enfermedad de Morquio). Ataques sincopales con convulsiones y espasmos, occurridos en niños pequeños sugieren la posibilidad de esta afeccion.

Las manifestaciones cerebrales pueden modificar desfavorablemente el pronostico de esta anomalia cardiaca. La extrema bradicardia con la consiguiente caida de la presion diastolica determina gran defecto en la circulacion cerebral. El papel de la anoxia cerebral en la produccion de la convulsion es considerado.

Se reporta un caso de sindrome de Stokes-Adams con bloqueo completo cardiaco en un niño de 19 meses cuyos ataques parecen coincidir con infecciones respiratorias. Clinica y radiologicamente se comprueba la existencia de congestion pulmonar. Desviacion asimetrica de las pulsaciones cervicales, contorno facial que altera su fisonomia. Se le practica electro-encefalograma.

Reposo absoluto, oxigeno y quimioterapia por si hubiera alguna afeccion intercurrente fueron usados durante el curso de los ataques.

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DEVELOPMENTAL PEDIATRICS: ITS TASK AND POSSIBILITIES

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SHORTLY after the American Board of Pediatrics was established in 1935, a basic requirement in *Growth and Development* was set up for specialty certification. When the medical history of the 20th century is written, we know this formal action will be regarded as a uniquely important event in the evolution of clinical medicine. Already we can see that a clinical science of development is in the making, and that the hygiene of the growing child is being envisaged in the dynamics of his growth. (We shall use the terms growth and development interchangeably for they are virtually synonymous.) Health is a somewhat static idea, unless by health we mean that condition which promotes optimal development.

Pediatrics is distinctive among all the specialties in three ways:

1. It is a specialty of general medicine.
2. It is directed to an age sector of life, rather than to an organ system.
3. It is basically interested in normality as well as disease.

Developmental Pediatrics is a form of clinical medicine which is systematically concerned with the diagnosis and supervision of child development, normal and abnormal.

DOCTRINE OF DEVELOPMENT

Development is a very usable concept—both for theoretic and for practical purposes. It is a unifying concept. It applies with equal force to body and mind. It resolves the false dualisms of psyche and soma. It also helps to resolve artificial distinctions between heredity and environment; between normal and abnormal; between structure and function. Development is an integrating concept. In fact, it is development which keeps the child from falling apart under the disrupting stress of excessive medical specialization.

Every newborn child traverses an indivisible, continuous cycle of growth. And for that very reason, the child remains the most cohesive force for the maintenance of family life in our democratic culture. The practicing pediatrician instinctively thinks of the child not only as the end product of eons of evolution, but also as a most important member of a family group; and by the way, also as the citizen of the future.

The cycle of child development begins with pregnancy. Biologically speaking, the cycle continues into the third decade of life. It embraces infancy, childhood, and youth. But from the standpoint of preventive and supervisory pediatrics, the first five years are of supreme, overshadowing significance. It is in this area that society is demanding a concentration of medical and social safeguards.

Responsive to this deep seated demand, the pediatrician and the general practitioner are becoming increasingly concerned with the prenatal as well as the early postnatal period of development. The developmental welfare, the nutrition, and to some extent even the immunization control of the infant-to-be begins before birth. A wise and benevolent obstetrician will freely grant that the pediatrician has a legitimate role in that part of

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maternal hygiene which is preparatory to parenthood. The psychologic orientation of the mother, and also of the father, to the problems of the neonatal period can be anticipated by suggestive guidance in the prenatal period. This guidance should not be assigned to some auxiliary specialty, but should be part of a continuous pediatric policy of developmental supervision.

First and foremost, the postnatal supervision will focus on nutrition and the biochemical status of the organism. But the regulation of nutrition, even at a physiologic level, inevitably leads to a diagnostic interest in the behavior characteristics of the infant—what he does, when he does it, and how he does it constitute a symptomatology. For the physician the behavior patterns of the infant are symptoms: to the parent they furnish clews and cues for intelligent child care. Behavior is the baby's language. He expresses himself in cries, and quiescence, in squirmings, in bodily attitudes, in facial tensions, in mouthings, in hand posturing, and eye movements. Spontaneous behavior thus becomes an indicator of his current well being and his immediate needs.

But not all of his needs are immediate. From month to month he moves onward through a cycle of growth. His long range needs must be considered in terms of that long range cycle. This is the task of developmental pediatrics, as a branch of clinical medicine which is systematically concerned with the diagnosis and the supervision of child development.

From the standpoint of clinical science, development is a process which yields to objective methods of investigation. It can be observed, measured and appraised in three major manifestations: (a) anatomic, (b) physiologic, (c) behavioral. Psycho-somatically no sharp distinction can be made between these three manifestations. The interaction of physical and mental factors is recognized. But if the mind as well as the body falls within the scope of pediatric medicine, chief attention must be given to the behavior patterns of the infant. His behavior characteristics constitute the most comprehensive index of his developmental status and of his developmental potentials.

Functions of a Developmental Examination

Fortunately, the developmental examination of infant behavior can be undertaken with relatively simple technics. Using the plain appurtenances of a crib, a table surface and a series of simple, toy-like test objects, it is possible, in a fraction of an hour, to elicit a rich array of behavior patterns which reveal the organization and the integrity of the child's total action-system. The behavior examination is conducted formally with precision of purpose.

In clinically experienced hands it serves five functions as follows:

1. It ascertains stages of maturity and rates of development in all types of infants, normal, subnormal, atypical, superior.
2. It yields differential diagnoses in relation to normality, amentia and specific developmental deficits and deviations.
3. It brings to light otherwise concealed neurologic defects and sensory impairments.
4. It renders objective information as to emotional and personality traits of the infant, and throws light on parent-child relationships. It serves to define therapy and guidance measures.
5. It implements a periodic type of developmental supervision.

These several functions represent an almost unoccupied area of preventive medicine. Can clinical pediatrics take over this vast domain?

Can it possibly do otherwise? From historic necessity the pediatric profession already holds the most strategic position in the whole scheme of medicine—it is situated at the portals of birth. It is medically responsible for the welfare of the newborn infant and his continuing growth. To the pediatrician, as specialist or as general practitioner, gravitate all the emotionally charged problems which concern the hygiene of early child development—the feeding problems of the normal infant with all their ramifications; the parent-child relationships; the gnawing anxieties if the child develops too slowly, or exhibits strange behaviors; the vague dread based on illnesses, disabling disease, physical defects, and traumatic injury, blindness, deafness, convulsive disorders, endocrine dysfunctions, congenital anomalies, and the varied cerebral palsies, devastating, selective and mild; and for good measure, the child born out of wedlock. All these problems have a cultural and a family setting; and, whether the child be normal or otherwise, the guardians of the child instinctively turn to the doctor for initial guidance and orientation. In one form or another all these problems involve the diagnosis and the medical supervision of early child development.

Developmental Supervision and Child Psychiatry

The demands for such supervision will grow more intense with the increasing intelligence of the public, and with the elaboration of health services already under way. The progress of the life sciences which deal with the biochemistry, the biophysics, the physiology and the pathology of growth will lead to more systematic protection of infant development. The world-wide study of cancer as a form of atypical growth, and the brilliant researches of experimental embryology, will almost certainly yield important knowledge for the control of normal organic growth. With new knowledge there will be refinement of technics and, we may hope that the technics can be applied with improvement rather than loss of human values.

The period of infancy is the primary responsibility of pediatrics. The child, to be sure, develops into the period of adolescence; but the professional status of clinical pediatrics would be strengthened by a concentration on the first years of life, and may be weakened by a dispersion over the entire growth span.

The present task of Developmental Pediatrics is clear enough; its possibilities, likewise, are so clear that one is tempted to paint the future with utopian colors. It is difficult to see how any other branch of clinical medicine is in a position, in itself or as a coordinator, to take over the vast work of mental hygiene implicit in the pediatric supervision of infants and young children. Pediatrics is a type of general medicine, and as such it includes psycho-somatic medicine. Its theory and principles are rooted in the biologic sciences. It is oriented to utilize their progressive discoveries with a minimum of ideology. Developmental Pediatrics, therefore, can bring into being a new type of child psychiatry with a realistic, integrative approach upon the dynamics of growth. The mental hygiene of infancy must of necessity reckon with the laws and mechanisms of development. Developmental methods of diagnosis and supervision constitute the very basis of a workable infant psychiatry.

A Developmental Unit for Postgraduate Training

These desirable possibilities can not be realized overnight, but they can be hastened through a few changes in the arrangements of medical education. Mere increase in the

number of curriculum hours for pediatrics will not solve the problem. We need a reorientation which will bring the normal child into the pit of the clinical amphitheater and which will raise normality to the dignity of a clinical subject. What I venture now to say is, with due qualification, addressed to the younger men who are going to shape the pediatrics of the future.

For sake of argument, I shall assume that normal development as well as disease and that mind as well as body fall within the scope of clinical pediatrics. Our view of the mind is downright monistic. The child comes by his mind in the same way that he comes by his body; namely, through orderly processes of growth. Accordingly, mental and physical welfare are indivisible, each reacting upon the other.

One may also assume that the private pediatric practitioner, or his equivalent in a diagnostic team, will be highly cognizant of the child not only as a biologic organism, but as a personality whose psychic structure is profoundly influenced by the cultural pattern of the home and the mores of the community.

On these premises the education of the general and of the developmental pediatrician will give great weight to the genetic aspects of science which interpret the evolutionary origins of man and his nature as infant, child, and adult. A broadened embryology might well become a key science, dealing in a coordinated way with the morphogenesis of embryo and fetus, the developmental anatomy of infant and child, the physiology of the fetus, the developmental chemistry of infancy, with special reference to maturity changes in allergy and metabolism, the biometry of bodily states in relation to maturity factors, the developmental aspects of physical anthropology. All this somatic knowledge can be brought into correlation with the embryology of behavior, the ontogenetic patterning of physiologic and psychologic functions—the patterning of autonomic reactions, and the growing forms of motor, adaptive, and personal-social behavior. Body types, psychic-constitution types, maturity and age norms, may be organized into normative criteria as aids to diagnosis. A clinical condensation of cultural anthropology would illuminate the status of the child as a member of the human family.

Such a program of professional training can be anticipated at undergraduate levels. It would come to an apex in a hospital training center, where the interne and resident would have one or two years of intimate participation in a diagnostic and guidance service dealing with the whole gamut of developmental problems in their human context. Post-graduate training should also take him into varied child care institutions and into the homes of the handicapped children, so that he will be confronted with the manifold personal and social implications of the problems.

This type of set-up envisages a functional diagnostic unit with a separate locus for developmental examinations and facilities for the naturalistic observation of infants and pre-school children. An adaptable therapeutic and guidance service for parent and child could be used to refine the prognosis and the recommendations. Emphasis would be placed on systematic follow-up study in order to individualize the care of handicapped and defective children. A periodic health service for normal infants, with intensive developmental surveys at a few selected age levels, would be part of a well rounded developmental unit. The Academy Study has already shown that well over half of the doctor's time is devoted to the supervisory care of the normal infant and child.

Under the auspices of such a unit the physician in training can be inducted into the art as well as the science of medicine. He will be compelled to understand the parents as well as the child, to detect their hopes, fears, beliefs, and mental conflicts. He will inter-

pret the needs of the child in relation to this complex of personal attitudes, and he will apply his psychologic insight in imparting diagnosis and advice. Thereby he acquires skill in the art of medicine; and also receives an education in social and moral responsibilities.

The program outlined is not impractical. In spite of its wide coverage it permits the simplification which comes with correlation and synthesis. The integrational potency of the concept of development will in itself consolidate rather than multiply the burdens laid on the physician in training.

The Outlook

If the progress of civilization is not halted, the social demands for health services in the first years of life will increase in volume and penetration. The growth of the nursery school movement, the downward extension of the public school system, the expansion of parent education, show the trend of the times.

The instability of marital relations is ominous, but the zeal with which parents pursue the physician for advice in the rearing of the young indicates the latent strength of the family. There is, moreover, a rising feeling that the usual well baby conference has reached a plateau of sub-efficiency, and that it should be vitalized and transformed into a more powerful educational agency. This could be done by incorporating a higher level of developmental diagnosis and supervision.

The almost systematic social neglect of the handicapped pre-school child is too well known. However, one state, Illinois, has recently set aside millions of dollars to reimburse local districts for the special education of their exceptional children. In a noteworthy pioneering statute this state responsibility has now been extended downward to the age of three years, to provide educational services for all types of pre-school handicapped children—the blind, the deaf, the crippled, the speech defective, the retarded, the under-vitalized, and the maladjusted.

We mention this legislation because it draws aside a curtain and brings into view the crucial years before three when the family and society inevitably turn to the physician for instruction in child care, for guidance and for wisdom. These years are too critical and emotionally too complex to be entrusted to agents and agencies not conversant with the deep human and medical issues which are involved. The pediatric physician remains the pivotal professional person in this sector of life. Here lies the challenge and the task. To young men the vista opens upon far reaching possibilities.

Spanish Abstract

Desenvolvimiento Pediatrico: Su Tarea y Posibilidades

La practica de la pediatria en America incluye tanto a los sujetos normales como enfermos y niños invalidos. Tanto los uno como los otros estan bajo la responsabilidad del pediatra y el medico de familia. Los padres no solo se interesan por la salud fisica sino al mismo tiempo por la salud mental en el crecimiento de sus hijos. Constantemente estan formulando preguntas a fin de obtener el mas apropriado consejo para la guia de los mejores metodos en el cuidado y entrenamiento de estos niños normales retrasados o lisiados. La tarea del pediatra es resolver estas demandas con el fin de lograr la mas amplia proteccion del niño. La proteccion debe empezar por los cuidados nutritivos y fisicos pero debe tambien extenderse al cuidado mental de estos sujetos.

El desarrollo de la pediatria esta especialmente relacionado con el diagnostico, cuidado y supervision del desarrollo del niño en todas sus etapas de manera de asegurar una vigilancia medica del mismo. Este desarrollo se refiere no solo a los signos fisicos de las distintas enfermedades sino que tambien comprende de una manera destacada los problemas relacionados con la conducta y su

relacion con los cambios de crecimiento. Los cambios pueden ser diagnosticados a traves de apropiadas pruebas de conducta las cuales van dirigidas a revelar el grado de madurez y eficiencia del sistema nervioso.

El uso sistematico de las pruebas encaminadas al examen de la conducta del niño es particularmente importante en los primeros tres años de la vida. Estos primeros años son los mas favorables para el establecimiento de la salud mental y para promover las mejores relaciones entre los padres y los niños. Es tambien periodo critico en que se descubren defectos y desviaciones, por ejemplo alteraciones visuales y auditivas, alteraciones motoras en general, lesiones cerebrales, retardo mental y defectos en la personalidad.

Un diagnostico temprano nos lleva a introducir metodos de tratamiento y reglas especiales en la guia de estos sujetos. La clinica pediatrica representa una estrategica posicion para desarrollar desde ella medicas preventivas en el extenso campo de la higiene mental. Los metodos diagnostico desde este punto de vista serian incorporados a la pediatria general y pueden ser tambien aplicados en escala mas especializada en centros apropiados de salud, hospitales de enseñanza, unidades sanitarias, etc.

El desarrollo de los metodos de diagnostico y supervision de estos sujetos constituye la base mas importante en el trabajo de las clinicas psiquiatricas infantiles. Este grado de especializacion en el desarrollo pediatrico aporta una nueva forma de psiquiatria infantil muy necesitada para la practica de diagnostico diferencial de los complejos casos de defectos y desviaciones de orden mental. La amplia tarea del desarrollo pediatrico es por lo tanto vasto campo en la higiene mental preventiva en el que comprende naturalmente tanto de los niños normales como aquellos que se desvian en grados variados de la anormalidad.

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USE OF MESOXALYL UREA (ALLOXAN) IN TREATMENT OF AN INFANT WITH CONVULSIONS DUE TO IDIOPATHIC HYPOGLYCEMIA

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INTRODUCTION

THE present communication is concerned with studies on an infant suffering from severe convulsions of hypoglycemic origin. For reasons outlined below the relatively untried chemotherapeutic agent, mesoxalyl urea (alloxan) was used. There is experimental evidence in animals that intravenously administered mesoxalyl urea destroys the beta cells of the islets of Langerhans and produces permanent diabetes.[1-5] While the drug has been used in a few human patients[6-10] its reported effects have been variable. In this patient it appeared to exert a beneficial influence. The following is, therefore, submitted with the hope that it may aid others interested in determining the potential clinical usefulness of this drug in similar types of patients.

HISTORY, EXAMINATION AND INITIAL STUDIES

An eight-month-old baby girl was admitted with the chief complaint of intermittent convulsions. When the child was five months old, the first episode of the present illness occurred. It was characterized by the development of a vacant, disoriented expression and upward rolling of the eyes, lasting about eight minutes. At about three week intervals thereafter she had somewhat similar disturbances which had as an additional characteristic, twitching of the facial muscles. The fourth of these was of much longer duration than any of the preceding. During it the patient maintained an almost constant staring expression for hours and in addition suffered two or three periods of tonic and clonic convulsions of the extremities. After three days of unsuccessful attempts at therapy she was referred to this hospital.

On physical examination she was seen to be a large and obese (10 kg.), tall (72 cm.) infant who was apparently comatose, lying flat in bed and staring fixedly into space. From time to time one or the other extremity twitched for a few moments. She was afebrile. The skin was pale and sweaty. The head was of normal size (circumference 46.5 cm.); the fontanelles and sutures were closed. The eyes tended to follow a bright light but otherwise moved very little. The pupils were very small in diameter. The eyegrounds were normal. There was no evidence of respiratory or other infection. The neck was supple. The heart and lungs were not remarkable. The liver was palpable about 1 cm. below the costal margin. All the reflexes were hyperactive. The remainder of a detailed physical examination revealed nothing of note.

Blood counts, urinalysis, Hinton and tuberculin tests, lumbar puncture and spinal fluid culture, determinations of the serum non protein nitrogen, total protein, calcium, inorganic phosphorus, alkaline phosphatase and CO_2 content as well as roentgenograms of the skull and long bones gave essentially normal results (Table I). Considered in conjunction with the clinical examination they tended to rule against the possibility of such causes of convulsions as infection, intracranial lesions, hypocalcemic or alkalotic tetany, lead poisoning and renal disease. One the other hand, valuable positive information was provided by measurements of blood and spinal fluid sugar concentrations.

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TABLE I

RESULTS OF DIAGNOSTIC STUDIES
(The methods used are listed elsewhere[11])

Urinalysis:	No reducing agents (sugar), albumin, acetone, bile or abnormal sediment.	
Spinal Fluid:	Pressure normal, crystal clear, colorless, total protein 13 mg./100 cc., sugar 34 mg./100 cc., 2 lymphocytes per cmm.	
Serum:	Non-protein nitrogen	22 mg./100 cc.
	Total protein	5.7 gm./100 cc.
	Calcium	9.9 mg./100 cc.
	Inorganic phosphorous	4.0 mg./100 cc.
	Cholesterol	139. mg./100 cc.
	Alkaline phosphatase	5.6 Bodansky units
	Sodium	144 mEq./L.
	Potassium	5 mEq./L.
	Chloride	100 mEq./L.
	Bicarbonate	25.8 mEq./L.
Response of blood sugar to 0.1 cc. 1:1000 epinephrine: control—100, ¼ hr.—100, ¾ hr.—199 mg./100 cc., respectively		
Roentgenograms:	Skull and long bones free from abnormalities. Intravenous pyelograms—no renal abnormality or displacement of kidneys by suprarenal tumor. Pneumoencephalogram—see Fig. 3.	

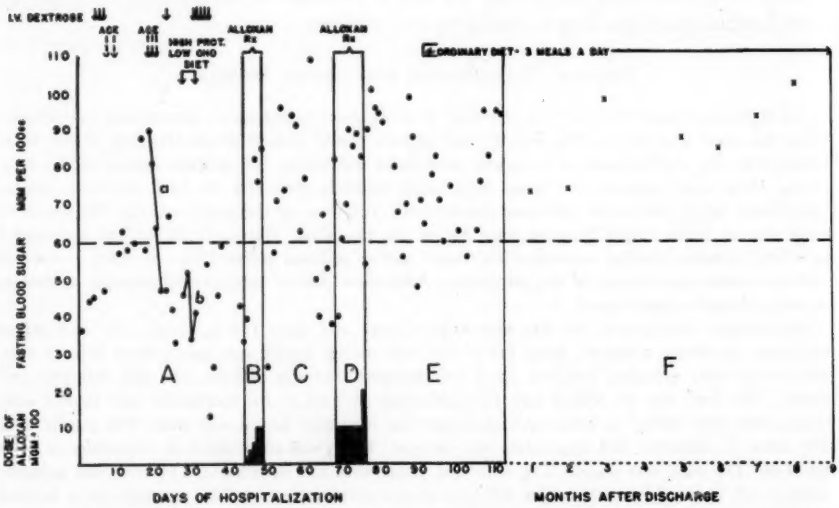

FIG. 1. Fasting blood sugar concentrations (ordinate) plotted against time (abscissa) before, during and after mesoxalyl urea therapy. Each black circle represents the value for one day. The interrupted horizontal line intersecting the ordinate at 60 mg./100 cc. represents the approximate lower limit for normal blood sugar concentrations.

It will be noted that the hospital stay was divided into five periods labeled A through E and that there was one period of observation after the discharge labeled F. During period A as shown at the top of the chart, the patient frequently received intravenous dextrose and in addition received adrenal cortical extract (ACE) during two brief periods. The blood sugar values obtained during the second period of ACE administration underwent a progressive fall as illustrated by curve "a." Also in period A she was placed on a high protein, low carbohydrate diet and the values obtained during this interval are illustrated by curve "b." The solid black area at the bottom of the chart in periods B and D respectively indicate mesoxalyl urea doses according to the scale at the bottom of the left hand ordinate.

The blood sugar concentration measured while the patient was having a convulsion was found to be 34 mg./100 cc. blood, a value definitely in the hypoglycemic range (normal range by method used is 70 to 100 mg./100 cc. blood).[12] The concentration of sugar in the spinal fluid also was abnormally low (34 mg./100 cc. fluid) as were a number of fasting blood sugar values taken in the morning before the first feeding (see Figure 1). The observations essentially established the diagnosis of hypoglycemic convulsions. This was confirmed on numerous occasions by the response of the patient to the ingestion of sweetened fluids or to the intravenous administration of dextrose solutions. Shortly after the administration of sugar the convulsions ceased and the patient began to awaken from the comatose state which prevailed before therapy.

Further Diagnostic Studies

In an effort to discover the reason for this child's hypoglycemia, studies designed to rule out certain causes of hypoglycemia[23, 24] were carried out (Table II). A rise of 99 mg./100 cc. blood in

TABLE II

Factors Responsible for Maintenance of Normal Blood Glucose Concentrations[13–24]

A. *Factors tending to elevate blood glucose*
   1. Assimilated carbohydrate
   2. Hepatic glycogenolysis
   3. Gluconeogenesis from protein and ? fat
      Adrenal cortical hormones (11-oxycorticosteroids)
   4. Anterior pituitary factor

B. *Factors tending to lower blood glucose*
   1. Tissue utilization
   2. Renal glycosuria
   3. Galactosemia
   4. Insulin

C. *General regulatory influence*
   1. Central nervous system

blood sugar following epinephrine (Table I) ruled against a primary disturbance in hepatic glycogenolysis. The possibility of adrenal cortical hormone deficiency was explored by a therapeutic test with adrenal cortical extract (12.5 rat units—5 cc. aqueous extract—every four hours subcutaneously). As shown by curve "a" of Figure 1, this presumably adequate dosage failed either to relieve or prevent hypoglycemia. Moreover she had no other signs of hypoadrenocorticism. Though a disturbance in the pituitary could not be ruled out, at least nothing suggestive of panhypopituitarism or of a pituitary tumor could be demonstrated.

With respect to Section B, Table II, the absence of reducing agents in the urine ruled out glycosuria and also galactosuria which is a characteristic of patients with galactosemia. There was no satisfactory method for estimating the concentration of insulin in this child. While the glucose tolerance tests recorded in the left hand section of Figure 2 were compatible with a diagnosis of hyperinsulinism, they could not be considered diagnostic thereof. The possible existence of an adenoma of pancreatic islet cells was investigated further by means of an exploratory laparotomy. The pancreas was carefully exposed and inspected, but no tumor nodules could be found. A small biopsy specimen obtained from the tail of the organ showed no evidence of hypertrophy or hyperplasia of the islets of Langerhans. Inspection of the liver and palpation of the adrenal glands at laparotomy revealed no gross abnormalities.

With relation to Section C, Table II, the possibility of so-called "functional hypoglycemia" was studied by modifying the diet. In this condition, the hypoglycemia ordinarily develops a few hours postprandially and is thought to be an over reaction to alimentary hyperglycemia. The period of hypoglycemia is of relatively short duration and tends to correct itself spontaneously. Functional

hypoglycemia can be avoided by eating low carbohydrate meals. Accordingly, the patient was placed on a low carbohydrate, high protein, high fat diet for a trial period of three days. During this period (curve "b", Period A, Figure 1) the fasting blood sugar concentrations fell and the patient became so much worse that it became necessary to institute intravenous dextrose therapy. Thus the patient's response appeared inconsistent with a diagnosis of the ordinary type of functional hypoglycemia. On the contrary, the factor operating to lower the blood sugar appeared not only to be uninfluenced by meals, but also to be very potent. This was illustrated by the fact that on occasions even two hourly oral feedings of whole milk with 10% carbohydrate added failed to prevent hypoglycemia manifestations of such severity as to require constant intravenous dextrose infusion for alleviation.

In summary, therefore, it was not possible to determine accurately the cause of this child's tendency to lowered blood sugar values. There remained unexplored the central nervous system; this will be considered below.

Therapeutic Considerations

One approach to therapy was suggested by the thesis that removal of the insulin factor should tend to result in a rise in the blood sugar concentrations from hypoglycemic to

Fig. 2. Pneumoencephalograms on present patient. Note marked internal hydrocephalus.

normal levels just as, conversely, the administration of insulin tends to lower elevated blood sugar values more or less irrespective of the cause of hyperglycemia. Subtotal pancreatectomy was, therefore, considered, but was not performed for two reasons. First, it was not considered a sure cure for hypoglycemia in this type of patient,[25] and the removal of a major source of digestive enzymes in a child of this age did not seem desirable. Second, the alternative of mesoxalyl urea therapy appeared worthy of trial.

Mesoxalyl Urea Administration to Present Patient

The child was given two courses of mesoxalyl urea therapy as follows. The drug* was dissolved in a solution of 0.85 gm. sodium chloride/100 cc. water at a concentration of between 1 and 2 gm./100 cc. The solution containing the mesoxalyl urea was administered intravenously at a rate of approximately 2 cc./min. Immediately following its administration the patient received through the same needle about 300 cc. of 10% dextrose at a rate of approximately 1 cc./min. During and after the period of administration the patient was closely observed for changes in general appearance suggestive of nonspecific toxic reaction or of hypoglycemia. It may be stated here parenthetically that no untoward reactions were observed at any time.

The doses and effects of mesoxalyl urea therapy are recorded in Figures 1 and 2. It can be seen that during the latter part of Period A, Figure 1, the fasting blood sugar values were abnormally low and appeared to show a downward trend. During Period B, Figure 1, she was given the drug in seven daily doses of 10, 20, 40, 60, 100, 100, and 100 mg./kg. per day. It can be seen that during this period the fasting blood sugar values increased appreciably. Not wishing to induce a diabetic state, mesoxalyl urea therapy was discontinued after a total dose of 3.3 gm. had been given. In the early part of Period C, Figure 1, the blood sugar values were with one exception essentially within normal limits and the patient was clinically improved as evidenced by freedom from symptoms of hypoglycemia. An apparent improvement in the glucose tolerance (Post-alloxan I, Curve "a," Figure 2) was also noted. These improvements permitted a change in dietary regime from four to six hourly feedings and finally to a schedule of three meals a day. Such a regime would have resulted in almost constant hypoglycemia prior to mesoxalyl urea treatment. However, on about the fourteenth day of Period C the fasting blood sugar values began to fall and symptoms of hypoglycemia reappeared. A repeat glucose tolerance test (Curve "b," Post-alloxan I, Figure 2) showed a reversion towards pretreatment values, especially towards very low values several hours postprandial. Accordingly the patient was given intravenously 1 gm. of mesoxalyl urea (or 100 mg./kg.) daily for seven days and 2 gm. on the eighth day (Period D, Figure 1). Again the response was encouraging as evidenced by a disappearance of clinical signs of hypoglycemia and an upward trend in the fasting blood sugar values. The improvement was also reflected in a more nearly normal glucose tolerances test (Post-alloxan II, Figure 2). It may be significant that the fasting blood sugar values tended to become stabilized at about 90 mg./100 cc. blood rather than showing a tendency to rise to hyperglycemic levels.

The subsequent course of the patient has been satisfactory from the point of view of the disturbance in blood sugar. On an ordinary diet of three meals a day she has had no further episodes of hypoglycemia. The majority of blood sugar values obtained during Periods E and F (Figure 1) were within normal limits. Furthermore, glucose tolerance tests obtained after the second course of mesoxalyl urea (Figure 2) shows no tendency to postprandial or fasting hypoglycemia such as was observed prior to therapy.

* Mesoxalyl urea is a pyrimidine related to and obtainable from uric acid. When injected into animals this chemical produces a selective destruction of the beta cells in the pancreatic islets of Langerhans and produces diabetes. The mesoxalyl urea (alloxan) used in this patient was kindly supplied by the American Cyanamid Company and before use it had been ascertained that a single dose of 150 mg./kg. produced the diabetogenic effect when injected into a normal rabbit.

As intimated above, the administration of mesoxalyl urea was not complicated by any clinically evident toxic manifestations. A number of white blood cell counts, hemoglobin determinations and urine examinations also failed to reveal any important changes.

Subsequent Course

While there were no symptoms of hypoglycemia after the mesoxalyl urea therapy, the patient did continue to have disturbances referable to the central nervous system. These were of two types: one was characterized by several episodes of generalized convulsions

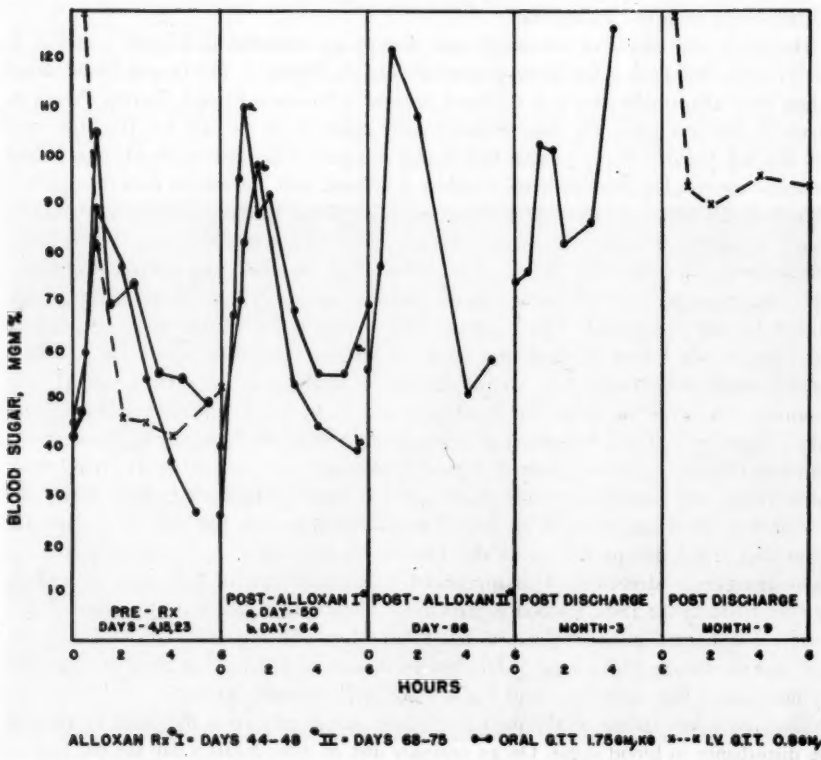

Fig. 3. Dextrose Tolerance Tests. The ordinate gives blood sugar concentrations; the abscissa, time in hours. The days and months indicated near the bottom of the chart correspond to those of Figure 1.

in association with fever and upper respiratory infections. These convulsions differed from those observed earlier in that the blood and spinal fluid sugar values were normal or elevated and in that the patient did not show the restlessness and tendency to eye rolling noted with the earlier hypoglycemic episodes. Also in contrast to the earlier hypoglycemic convulsions, they could be controlled by such sedative therapy as 5 cc. of paraldehyde intramuscularly. Furthermore, once controlled they did not tend to recur as they had when she showed hypoglycemic tendencies, thus suggesting a different origin.

Further support of this thesis was provided by the gradual development of a second and new type of disturbance characterized by mild spastic paralysis of the right hand and leg. Electroencephalograms made during the periods of hypoglycemia were reported by Abbott to show symmetrical and diffuse high-voltage slow activity compatible with hypoglycemia. Later electroencephalograms taken during the normoglycemia phase after the first course of mesoxalyl urea (Period C, Figure 1) showed marked improvement with activity somewhat slower than normal for age but without localized abnormalities. However, a record taken 3 months after discharge from the hospital (Period E, Figure 1) disclosed true dysrhythmic activity on the left side of the head with much normal activity

FIG. 4. (MGH # 387877) This 7½ year old boy developed diabetes mellitus at the age of two years. Up to that time his growth, maturation and general health had been satisfactory. During the first two years of diabetes he was treated in another clinic with relatively large doses (16 units) of protamine insulin only. Presumably as a consequence of this type of therapy he suffered numerous insulin reactions. At the age of seven years he came to this clinic with the chief complaints of diabetes mellitus and behavior problem. At that time he was receiving 12 units of protamine and 8 units of regular insulin before breakfast and was free from reactions. Complete physical examination revealed no abnormalities. The intelligence quotient was 111. While the neurologic examination also revealed no definite abnormalities it was believed that his behavior pattern was unusual and might be a manifestation of diffuse brain damage secondary to episodes of insulin induced hypoglycemia. At 7¼ years he suffered the first of a series of generalized convulsions. Simultaneously he commenced to show evidences of gradual intellectual deterioration. Pneumoencephalography performed at 7½ years revealed enlargement of the lateral and third ventricles. There was no gross evidence of cortical atrophy or of a causative lesion. The left lateral ventricle appeared larger than the right. A series of electroencephalograms likewise showed increasing abnormalities becoming most marked over the left occiput. In the three years subsequent to these studies he has become aphasic and grossly mentally retarded. While impossible to prove, the foregoing sequence of events was presumably due to the repeated insulin reactions from which he suffered especially between the ages of two and four years.

especially on the right side. Taken together these findings suggested that the patient had developed a grossly evident disturbance of the left cerebral cortex during the latter part of the 12 month period of observation. The pneumoencephalograms shown in Figure 3 indicate its extent and locality.

Comments

The relation between mesoxalyl urea treatment and relief from hypoglycemia in this patient appear too close to be considered fortuitous. On the other hand, it was not possible to prove by examination of the pancreas or by measurements of the concentration of insulin in the blood stream that the administered mesoxalyl urea caused either a relative or absolute hypoinsulinism. Such information would be of the greatest interest and value.

While no toxic manifestations were observed in the present case, it is of importance to emphasize that severe toxic reactions including acute liver necrosis and death have been reported by others.[6-8]

The possible relations in this patient between the hypoglycemia and the central nervous system lesion also fall into the realm of speculation. Cases have been described wherein the available evidence suggested that demonstrable central nervous system defects were primary and were responsible for disturbances in the regulation of blood sugar concentrations.[16] On the other hand, there also is evidence which shows that a primary hypoglycemia of sufficient severity to cause convulsions may result in appreciable brain damage.[26-28] This point is further illustrated by Figure 4 which portrays changes in brain structure which apparently developed following repeated overdoses of insulin in a child with diabetes mellitus. Whichever etiologic thesis be correct in the present patient, it is clear that severe, recurrent hypoglycemia may damage the brain extensively.

Summary and Conclusions

The case history of an eight-month-old infant with severe convulsions due to idiopathic hypoglycemia is described. Because of the poor prognosis and lack of other certain means of therapy, treatment of the hypoglycemia by means of mesoxalyl urea was undertaken with apparent success.

It is concluded that mesoxalyl urea, though a potentially dangerous drug, may be worthy of further cautious trial in patients of the type described here.

References

1. Bailey, C. C. and Bailey, O. T., Production of diabetes mellitus in rabbits with alloxan, J.A.M.A. **122**:1165, 1943.
2. Dunn, J. S. and McLetchie, N. G. B., Experimental alloxan diabetes in rat, Lancet. **2**:384, 1943.
3. Goldner, M. G. and Gomori, G., Alloxan diabetes in dog, Endocrinology **33**:297, 1943.
4. Banerjee, S., Alloxan diabetes in monkeys, Lancet. **2**:658, 1944.
5. Brunschwig, A., Allen, J. G., Goldner, M. G., and Gomori, G., Alloxan, J.A.M.A. **122**: 966, 1943.
6. Brunschwig, A., Allen, J. G., Owens, F. M., Jr., and Thornton, T. F., Jr., Alloxan in treatment of insulin producing islet cell carcinoma of pancreas, J.A.M.A. **124**:212, 1944.
7. Brunschwig, A., and Allen, J. G., Specific injurious action of alloxan upon pancreatic islet cells and convoluted tubules of kidney. Comparative study in rabbit, dog and man; attempted chemotherapy of insulin—producing islet cell carcinoma in man, Cancer Research **4**:45, 1944.
8. Conn, J. W., Hinerman, D. L., and Buxton, R. W., Effects of alloxan upon human pancreas, J. of Lab. & Clinic Med., **32**:347, 1947.
9. Rynearson, E. H., Personal communication.

10. Flinn, L. B., Minnick, E., and Gay, D. M., Alloxan in treatment of islet cell carcinoma of pancreas with liver metastases, Ann. Int. Med. **26**:936, 1947.
11. Rourke, G. Margaret, MacLachlan, Elsie A., and Butler, A. M., Normal laboratory values, New England J. Med. **234**:24, 1946.
12. Folin, O., Micro method for determination of blood sugar, New England J. Med. **206**:727, 1932.
13. Wauchope, G. M., Hypoglycemia, Quart. J. Med. **2**:117, 1933.
14. Kramer, B., Grayzel, H. G., and Solomon, C. I., Chronic hypoglycemia in childhood, J. Pediat. **5**:299, 1934.
15. Mason, H. H., and Turner, M. E., Chronic galactemia; with studies on carbohydrates, Am. J. Dis. Child. **50**:359, 1935.
16. Darrow, D. C., Mental deterioration associated with convulsions and hypoglycemia, Am. J. Dis. Child. **51**:575, 1936.
17. Conn, J. W., Advantage of a high protein diet in treatment of spontaneous hypoglycemia, J. Clin. Investigation **15**:673, 1936.
18. Rector, J. M., and Jennings, R. E., Functional hypoglycemia of childhood, with particular reference to recurrent convulsive manifestations, Am. J. Dis. Child. **53**:1012, 1937.
19. Russell, J. A., Relation of anterior pituitary to carbohydrate metabolism, Physiol. Rev. **18**:1, 1938.
20. Long, C. N. H., Katzin B., and Fry, E. G., Adrenal cortex and carbohydrate metabolism, Endocrinology **26**:309, 1940.
21. Conn, J. W., Spontaneous hypoglycemias, J.A.M.A. **115**:1669, 1940.
22. Soskin, S., Blood sugar: its origin, regulation and utilization, Physiol. Rev. **21**:140, 1941.
23. Mason, H. H., and Anderson, D. H., Glycogen disease, Am. J. Dis. Child. **61**:795, 1941.
24. Stetten, DeWitt, Jr., Endocrine regulation of carbohydrate metabolism, J.A.M.A. **132**:373, 1946.
25. Holman, E., and Railsback, O. C., Partial pancreatectomy in chronic spontaneous hypoglycemia, Surg. Gynec. & Obst. **51**:591, 1933.
26. Grayzel, D. M., Changes in central nervous system resulting from convulsions due to hyperinsulinism, Arch. Int. Med. **54**:694, 1934.
27. Baker, A. B., Cerebral damage in hypoglycemia, Am. J. Psychiat. **96**: 109, 1939.
28. Baker, A. B., Cerebral lesions in hypoglycemia; some possibilities of irrevocable damage from insulin shock, Arch. Path. **26**:765-76, 1938.

SPANISH ABSTRACT

Uso del Mesoxalil Urea (Alloxan) en el Tratamiento de Niños con Convulsiones Debidas a Hipoglicemia Idiopatica

La historia de un niño de ocho meses con severas convulsiones debidas a hipoglicemia idiopatica es aqui descrita. El pronostico malo y la falta de efectivos metodos terapeuticos en el tratamiento de la hipoglicemia lleva al ensayo del uso del mesoxalil urea en este caso con aparente exito.

Se concluye que el Alloxan, de quien se piensa que es una droga peligrosa puede ser sin embargo con las precauciones debidas utilizado en el tratamiento de pacientes del tipo del que aqui se describe.

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BRAIN TUMORS IN INFANCY
A Report of Seven Cases

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SINCE intracranial tumors in infants are uncommon, they often go unrecognized even though their importance has been emphasized.[1-4] Infancy is considered generally as extending up to 24 months of age[5] and within this age period the opportunity has presented itself for the study of a group of seven verified intracranial tumors. It is the purpose of this communication to describe the findings in this series of cases and to describe a unique experience of encountering an hemangioblastoma of the cerebrum in an infant in whom the tumor was, so far as could be determined, completely removed.

Most physicians think of brain tumors in terms of the features seen so often in children and adults; and, therefore, such lesions in infants frequently are incorrectly diagnosed.[6, 7, 8] Such errors are due to the fact that the signs observed in infants with brain tumors vary considerably from those in older individuals. The presence of brain tumors in infants is masked for the following reasons:

(1) Most infants below the age of one year do not walk or talk and make few attempts at purposeful movements. Therefore, they cannot complain of headache or blurred vision. Neither can ataxia or past pointing be readily recognized.

(2) Because of ununited sutures, the pressure effects of an expanding intracranial tumor are diminished. Papilledema may be slight or not present. Globus[2] reported its presence in five out of eleven cases. Gross[6] found it in five out of nine cases. This buffering effect of the pliant skull may also account for the absence of vomiting. Hydrocephalus and a wide bulging anterior fontanelle may frequently be the first physical signs of a brain tumor in infancy. Hydrocephalus was present in each one of Gross' cases. Radiographic examination of the skull may reveal widened suture spaces and also occasionally thinning of the bone at the site of the tumor. MacEwen's cracked-pot sound on percussion of the head may be present.

(3) The diagnosis of a brain tumor may be confused by the presence of fever, vomiting, convulsions, listlessness and somnolence. These are non-specific signs of illness in infants. Because of their frequency in other systemic diseases, the possibility of central nervous system affliction is frequently overlooked.

A review of the literature reveals that there is no striking predilection of the tumors in infants for the subtentorial rather than the supratentorial regions.[1-4, 6, 10, 11] In recent years it has been generally agreed that the gliomas comprise the greatest proportion of infant brain tumors.[1, 2, 9, 10, 12] Marburg[12] concluded that the tumors of completely immature tissue usually occurred in the earlier years; whereas, tumors of more mature tissue occurred in the later childhood. Table I lists the types of tumors found

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in the larger series reported in infants. Meningeal tumors are rare in infants. They are usually of the sarcomatous type when they do occur.

Many tumors in infants and children were reported as tuberculomas at the end of the last century and the early 20th century. It was thought that about 50% of tumors in childhood were tuberculomas. In 1937 Stern[4] reported only 6% as tuberculomas. In this country, these findings at present are even more infrequent. The diminution in this type of tumor is undoubtedly due to improved diagnostic and public health measures.

The medulloblastomas, frequently listed in the older literature as round cell sarcomas, deserve special consideration from the diagnostic viewpoint. Bailey and Cushing[13] emphasized the tendency of this undifferentiated tumor to invade the meninges and produce implants. It is, therefore, possible to have medulloblastoma cells circulating in the cerebrospinal fluid. Since these cells bear some resemblance to lymphocytes, the mistaken

TABLE I

	Gross	Globus	Wollstein Bartlett	Bailey	Stern
Ependymoma	3	2		2	1
Medulloblastoma	3	1			1
Astrocytoma	1		6	1	3
Astroblastoma	1				
Spongioblastoma				1	1
Glioblastoma Multiforme					1
Spongioneuroblastoma		1			
Subependymal Glioma		1			
Pinealoma		2		3	
Pineablastoma	1				
Gliosarcoma			1		
Sarcoma				1	2
Meningeal Tumors				2	1
Colloid Cyst		1			
Metastatic		2			
Glioma Unclassified				2	
Tuberculoma					2

diagnosis of meningoencephalitis may be made. The signs and symptoms of meningoencephalitis may occur in cases of medulloblastoma. Walt[14] reported such a case in a 21-month-old infant in which the correct diagnosis was made; however, since round refractile cells with eccentric nuclei were seen in the spinal fluid, some of these cells were present in clumps and represented medulloblastoma cells.

The onset of symptoms and signs of a brain tumor may be acute, or slow and progressive. The rapid onset and course may be caused by swelling or edema of the tumor, hemorrhage into the tumor, interference of the blood supply of the tumor, or a precipitous occurrence of an obstructive hydrocephalus due to pressure of the tumor.[15]

The spinal fluid findings are not constant. The medulloblastoma has already been mentioned as capable of releasing abnormal circulating cells in the subarachnoid space. Pleocytosis in the spinal fluid also may result from aseptic meningeal reaction to necrosis of brain or tumor tissue near the ventricles. The protein content of the lumbar fluid may be normal or increased.[16]

The conditions which must be considered in the differential diagnosis include congenital hydrocephalus, subdural hematoma, tuberculous meningitis, brain abscess, encephalitis, lead poisoning and vomiting due to other causes so frequently seen in infants.

The following are the case records of six infants under two years of age in whom brain tumors were found at operation or necropsy.* An additional case will be reported in which it was not possible to verify the histological diagnosis since the sections were not available for review.

Case Reports

Case 1: J. C., J.H. No. 300103. White male, aged 22 months. Hemangioblastoma of right temporo-parietal region. Paresis of left upper and lower extremities for two weeks. Tumor removed in its entirety with complete recovery.

This infant was admitted to the hospital on February 2, 1947. He was in good health until two weeks before admission when his mother noted that he was walking with a limp and that he seemed to drag his left leg. A few days later, he began to hold his left arm limply at his side. At the same time, the use of his left upper extremity appeared to have become reduced. He became very irritable and slept poorly. There was no vomiting, photophobia or loss of consciousness. The developmental history was normal.

Physical examination revealed a well nourished infant who did not appear acutely ill. He was very irritable. A cracked-pot sound upon percussion of the skull was elicited. The fontanelles of the skull were closed. There were no palpable patent sutures. The pupils of the eyes were round, regular and equal and reacted to light. There was fullness of the retinal veins with obliteration of the physiological cups and indistinctness of the disc margins. A mild left peripheral facial paralysis was present. The other cranial nerve functions appeared to be intact. The left upper and lower extremities were maintained in a frog-leg position. The left arm was weak. The grip of the left hand was poor. The infant rarely moved his left leg while in bed. When he walked, a pronounced limp of the left leg was present and he preferred bearing weight on his right leg. The left biceps, quadriceps and achilles tendon reflexes were hyperactive. The left abdominal reflexes were absent. Ankle clonus was not present. A positive Babinski sign was elicited on the left side.

On February 3, 1947, electroencephalography revealed evidence of electrical abnormality from the right cerebral hemisphere with a centro-parietal concentration. There was radiographic evidence of definite spreading of the coronal and sagittal sutures. The lambdoidal suture was slightly widened. The right side of the cranial vault was slightly thinner than the contralateral side. No abnormal calcific deposits were seen.

On February 7, 1947 a right fronto-parietal craniotomy was performed by Dr. I. M. Tarlov. The bone in this area was paper thin. The convolutions of the brain beneath the dura were very flat. A needle introduced to a depth of about 0.5 cm. from the surface yielded yellow fluid. Following an incision into the brain at this point, a large cystic cavity was disclosed. It contained about 60 cc. of yellow fluid which coagulated spontaneously. Along the anterior wall of the cavity was a brown, slightly nodular and very vascular tumor which was extremely tough. It measured about 3 to 4 cm. in diameter. Elsewhere the cavity was lined by slightly yellowish stained tissue that appeared to be brain. As far as could be determined, the entire tumor was removed.

The immediate post-operative course was satisfactory. By the sixth post-operative day, the infant was alert, cheerful and playful. He moved both left extremities. He was discharged to his home on the ninth post-operative day. At that time he used his left upper and lower extremities in better fashion than pre-operatively. His left hand was still weak. Slight weakness of the left facial muscles was still noted. He began to bear weight on his left lower extremity.

When last seen (about eight months after operation), he was cheerful and playful. He used all extremities equally well and all facial movements were normal. Recovery apparently was complete.

Microscopic examination of the tissue revealed that it was very vascular (Fig. 1). Blood vessels varied from spaces lined by endothelium or strands of connective tissue to large vessels with fully formed walls. There was relatively little intervascular tissue, some of which consisted of cuboidal or round cells. In some areas, these cells were identical with the lining cells of spaces which in

* An additional case, previously reported from this institution,[25] will not be discussed.

some instances contained blood. In Scharlach R preparations, fat laden cells were seen in the intervascular tissue.

The tumor certainly was a vascular one and doubtless was neoplastic rather than a congenital anomaly. It belongs in the category of hemangioblastomas.

Comment: The diagnosis of brain tumor in this infant was not difficult. His signs were characteristic of those usually associated with tumors which occur in older people. The paresis of the left upper and lower extremities, the exaggerated deep reflexes on the

FIG. 1 (Case 1).—Photomicrograph of an hemangioblastoma showing numerous blood vessels lined by endothelial cells. These cells are similar to the stroma cells (Hematoxylin and Eosin stain x150).

left side, absent left abdominal reflexes, the positive Babinski sign and the electroencephalographic findings were indicative of a lesion of the right cerebral hemisphere. The positive MacEwen's sign, papilledema and X-ray evidence of separated cranial sutures with thinning of the bone were secondary to increased intracranial pressure.

This was a most unusual case because the tumor proved to be an hemangioblastoma which occurs in the cerebrum uncommonly. In 1928, Bailey, Cushing and Eisenhardt[17] recorded several angioblastic meningiomas in the cerebrum which they considered as arising from the meninges. Histologically, the tumors are much the same as the hemangioblastomas. Usually, however, angioblastic meningiomas are of solid consistency; whereas, the hemangioblastomas of the cerebellum are usually cystic. Certainly there is a very close relationship, if not an identity of cell type between these tumors.

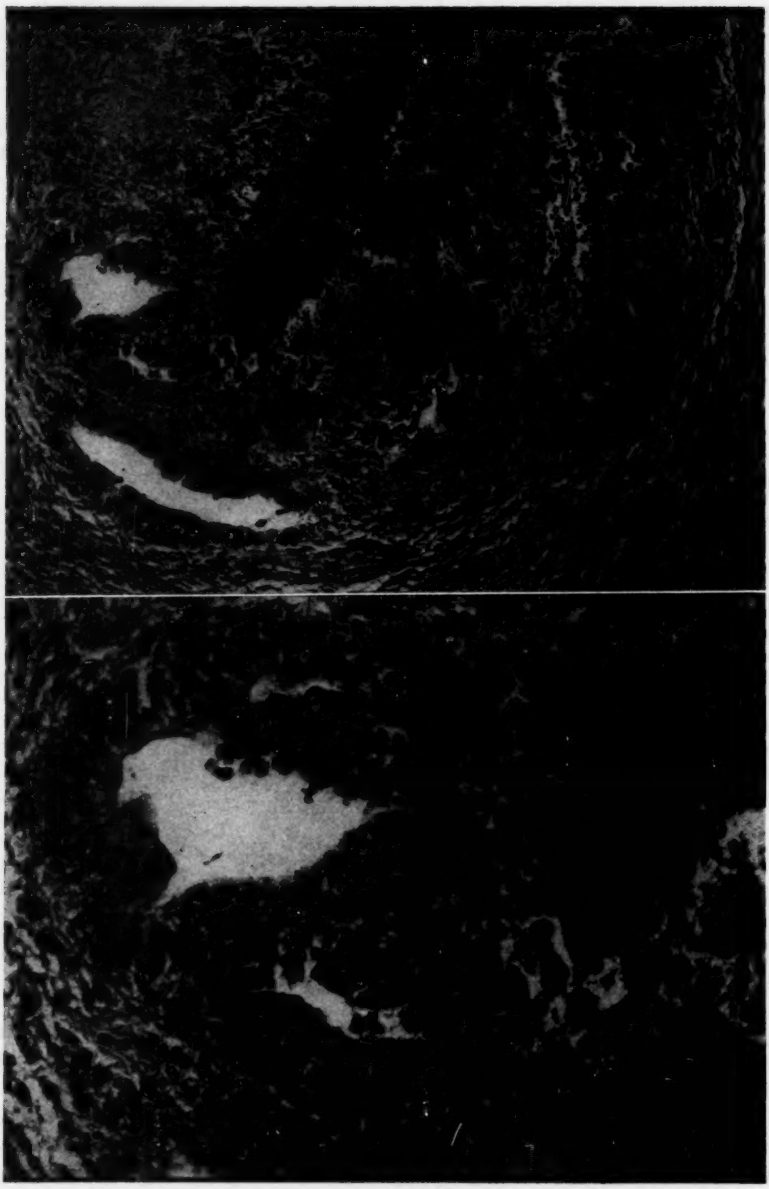

FIG. 2 (Case 2).—Photomicrograph of an ependymoma showing (A) the tendency for tumor cells to form cannular structures. An area of necrosis is seen, but this was not characteristic of the tumor. A high power view (B) shows cuboidal and columnar cells forming ependymal canals with a well formed basement membrane (Hematoxylin and Eosin stain. A:x150. B:x350).

Case 2: J.R., J.H. No. 213915. Male, aged 22 months. Ependymoma of posterior fossa partially removed at operation. Roentgen radiation subsequently given. Re-exploration one year later followed by immediate post-operative death.

A white male infant was admitted to the hospital on July 26, 1938. Five months prior to admission he fell to the ground but received no apparent head injury. He vomited once or twice at that time but improved spontaneously. Three months prior to admission, persistent vomiting developed and lasted for three weeks. A left internal strabismus was noted at that time. One month prior to hospitalization, he again began to vomit daily. This was not projectile in character. Subsequently, a staggering gait was noted. He was barely able to walk.

Physical examination revealed a fairly active infant who cried freely. He was unable to stand without assistance. MacEwen's sign and bilateral papilledema were present. The right pupil reacted sluggishly to light and was smaller than the left. Left internal strabismus was present. Motor power and gross sensation appeared to be normal. The tendon reflexes were hyperactive. Bilateral Babinski signs were elicited.

Fluid obtained on lumbar puncture was bloody. The initial pressure was 252 mm H_2O. Protein content was 17.5 mg./100 cc. of ventricular fluid. An area of calcification was seen in the suboccipital region to the right of the midline on radiographic examination. Ventriculography showed a symmetrical dilatation of the lateral and third ventricles, aqueduct of Sylvius and the anterior portion of the fourth ventricle. The posterior portion of the fourth ventricle was obliterated by a mass which was continuous with the previously described calcified area. The impression was that a large midline cerebellar tumor was present. On July 28, 1938, a suboccipital craniotomy was performed by Dr. Leo M. Davidoff. A tumor was found in the lower end of the vermis extending into the spinal cord. Total removal of the tumor was deemed unwise because of the poor condition of the patient. Forty-five hundred R. units of X-ray therapy were given post-operatively between August 26, 1938 and September 30, 1938. The patient was discharged on the 68th post-operative day, somewhat improved. Roentgentherapy totalling 4500 R. Units was applied between October 31, 1938 and December 21, 1938.

Microscopic examination of the surgical specimen exhibited variation in appearance in different areas. In most areas, the cells were of a cuboidal type in ring formation around clear canals (Fig. 2). In other areas, the cells were around blood vessels with a rather wide zone of cytoplasmic processes between the vessel wall and nucleus. In still other areas in a gold chloride sublimate preparation, the predominant cell was a small astrocyte. There was intermingling of these various cell types and patterns. Considerable calcification was present which in some areas appeared to have begun within the cells. The tissue was characteristic of an ependymoma.

The patient returned to the hospital on August 27, 1939, because of exaggeration of his previous symptoms and signs. Re-exploration was carried out on August 29, 1939 and a great deal of tumor tissue was removed from the cerebellum. During the operative procedure, his blood pressure fell. The procedure was interrupted and the wound was closed rapidly. He expired soon after the closure.

Necropsy was performed on August 29, 1939. The vermis and most of the cerebellar tissue was found to be missing. The tumor removal appeared to have been complete. The cerebral cortex, pons and medulla were intact. Sections of the cortex and pons were not remarkable. The cut surfaces of the medulla contained small hemorrhagic areas which measured up to 0.8 cm. in diameter. The remaining cerebellar tissue was red and purple, soft and friable. Histological examination provided no additional information except for areas of congestion and hemorrhage in the medulla.

Comment: The symptoms and signs in this case were rather typical of a tumor involving the mid-cerebellum and fourth ventricle. The vomiting, which need not be projectile and which is a frequent concomitant of intracranial tumors, was probably due to increased intracranial pressure or direct involvement of the medullary centers. X-ray of the skull revealed a calcified area in the suboccipital region. Sachs[18] and Fincher and Coon[19] found that the only tumors of the young age group which showed calcification were ependymomas. This case proved to be such a tumor. However, Bailey, Buchanan and Bucy[1] found that none of their cases of ependymomas exhibited calcifica-

tion. Air studies were helpful in localizing the lesion in this case. Operative results in this type of tumor are unsatisfactory even when the cells are of a mature variety because of the tendency of the tumor to invade the adjacent brain stem.

Case 3: W.S., J.H. No. 234020. White male, aged 21 months. Spongioblastoma polare between the optic chiasm and cerebral peduncles. Symptoms for one month. Diagnosis unsuspected. No localizing neurologic signs. Death on the 14th day of hospitalization.

The infant was admitted to the hospital on June 26, 1940. The birth history was normal. He apparently had been well except for retarded development of speech. One month prior to admission,

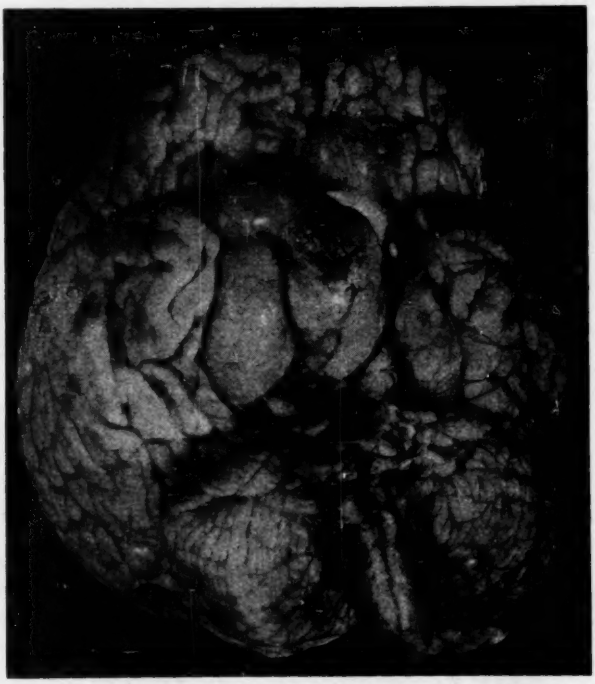

FIG. 3 (Case 3).—View of brain showing a large tumor (spongioblastoma polare) occupying the area between the optic chiasm and the cerebral peduncles.

the mother noticed that he fell to the floor while walking. He had fallen from a chair on two occasions, one year and one month prior to admission. He was unable to rise without assistance on each occasion. Three weeks prior to admission, he refused to stand at all and trembled when placed on his feet. In the following weeks, he also refused to sit up. He was anorexic and appeared to sleep more than usual. He not infrequently awoke from sleep crying.

The infant was exceedingly irritable but when undisturbed, he appeared to drowse off to sleep. When placed in an upright position, his lower extremities stiffened and all four extremities trembled. Mild spasticity of the legs was present. There was generalized hyperreflexia. Bilateral ankle clonus and Babinski signs were elicited.

A lumbar puncture revealed an initial pressure of 470 mm. H_2O. The protein content of the spinal fluid was 100.3 mg./100 cc. of fluid. The patient ran an elevated temperature which on a few occasions reached 40° C. Pneumoencephalography was performed on July 3, 1940. Tremendous

dilatation of both lateral ventricles was seen. His general condition remained unchanged and six days later, following a pre-agonal rise in temperature to 41.6° C, the infant expired.

The clinical impressions recorded included hydrocephalus, cerebral agenesis, Schilder's disease and cerebral sclerosis.

A complete necropsy was performed one hour after death. The brain weighed 1290 gm. and was fluctuant in consistency. There was a large lobulated tumor which measured 7 cm. in diameter (Fig. 3). It occupied the inferior aspect of the brain between the optic chiasm in front and the cerebral peduncles behind. The optic chiasm was displaced far to the left by the underlying tumor. The tumor was covered by a smooth and glistening capsule in which there were prominent blood vessels. Part of the tumor was cystic and contained amber-colored fluid. The external surface of the tumor was mottled yellow and gray. On sagittal section, the tumor extended superiorly

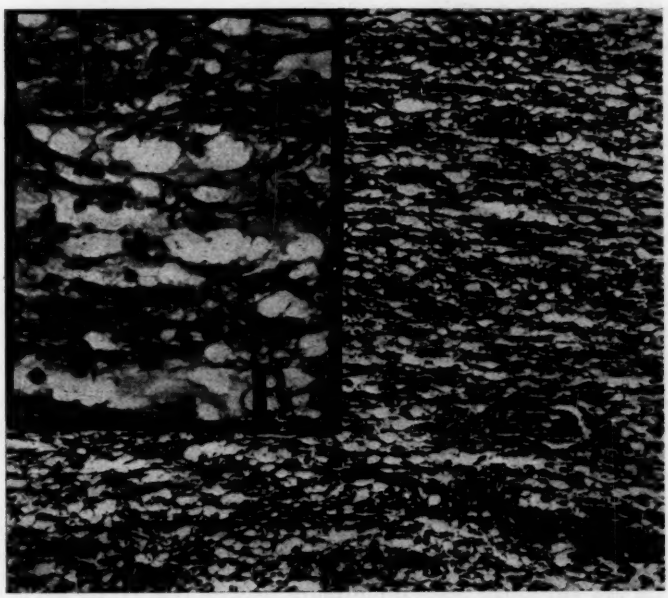

FIG. 4 (Case 3).—Photomicrograph of a spongioblastoma polare showing (A) the general architecture of the tumor. High power insert (B) reveals elongated cells with oval nuclei which in metallic impregnation sections proved to be polar spongioblasts (Hematoxylin and Eosin stain. A:x150. B:x350).

to compress the third ventricle. The tumor merged imperceptibly with the diencephalon and was poorly demarcated from it. The cut section was pink and gray mottled with yellow and red. The lateral ventricles were enormously distended when viewed from a single coronal section.

Histologically, the tumor consisted of elongated cells with oval or elongated nuclei and scant pink staining cytoplasm (Fig. 4). At one or both poles of the cells delicate processes arose. Small round cells with round clear staining nuclei and pink staining cytoplasm were also seen. A few short delicate processes arose from these. Around the blood vessels were concentric layers of tumor cells. In other areas were collections of extravasated blood. In the Laidlaw connective tissue preparations, the reticulin was seen only about the blood vessels and not in the tumor tissue. The cells comprising the bulk of the tumor resembled unipolar and bipolar spongioblasts. The histologic picture was that of a spongioblastoma polare.

Comment: This infant exhibited progressive difficulty in walking accompanied at a

later date by somnolence. These features and his spasticity were evidence of central nervous system disease. The fact that he not infrequently awoke from sleep crying may have been interpreted as a sign of pain. The presence of an elevated temperature in neoplasms of the brain has been repeatedly emphasized. Strauss and Globus[20] felt that the hypothalmus and the area about the third ventricle were the possible sites for heat regulation. They reported tumors of these areas which produced fever. In retrospect, the rather sudden onset, the rapidly progressive course and the elevated protein content of the cerebrospinal fluid were factors which might have led to the proper diagnosis. Bailey and Eisenhardt[21] found that this tumor most frequently involves the optic chiasm and next in order, the cerebellum and the brain stem. It is a slow growing tumor but the operative results are poor due to its inaccessibility.

Case 4: C.N., J.H. No. 259073. White male, aged 4 months. Astrocytoma of the midbrain. Clinically resembled congenital hydrocephalus. Diagnosis unsuspected. Death followed choroid plexectomy.

This infant was admitted to the hospital on October 31, 1942. He had been delivered with low forceps following a normal full term pregnancy. At birth his head measured 39.5 cm. During the four months of life, his head became progressively larger. The infant failed to gain weight for 2 months prior to admission. There was no history of paralysis or convulsions.

Physical examination revealed an enormously enlarged head which measured 61.5 cm. in circumference. The scalp veins were dilated. The fontanelles were enlarged and tense. He did not appear to see light. He moved all extremities. The lower extremities were spastic and held in adduction. The deep reflexes were hyperactive. Bilateral Babinski toe signs were elicited.

A ventricular puncture was performed on November 3, 1942 and the ventricle was reached one cm. from the scalp. It was felt that he had a congenital hydrocephalus. Operation was carried out on November 4, 1942 and the right choroid plexus was coagulated. As the dressing was being applied, the infant suddenly ceased breathing and was pronounced dead.

A complete necropsy was performed on November 6, 1942. The brain showed a markedly thinned cortex. It weighed 800 gm. On the floor of the right ventricle there was a small nodule of tissue, the surface of which was seared. The external surfaces of the cerebellum, midbrain and medulla were well formed. Coronal sections revealed great dilatation of the lateral and third ventricles. The third ventricle ended in a dimple at the superior portion of the midbrain. Serial sections through the midbrain revealed no evidence of the aqueduct. The fourth ventricle was of usual size and shape. The foramina of Luschka were small and patent.

Histological preparations revealed evidence of neoplasm in the mid-brain on one side of the aqueduct. The cells were spindle shaped and irregularly polygonal (Fig. 5). The area of tumor was irregular in shape and poorly demarcated from the surrounding tissue. The spindle shaped cells were large and had large elliptical shaped nuclei. A fine tail projected from each end of a spindle cell and some of these divided near the cell body. There were a greater number of irregular polygonal cells, varying in size and ending in several processes. These were clearly astrocytes. The tumor mass extended almost to the aqueduct, which was broken into slit like and round spaces by the irregular projections of the tumor. The tumor was an astrocytoma.

Comment: This young infant had progressive enlargement of the head since birth without localizing neurological signs. The spasticity and apparent blindness present in this case have been noted in congenital hydrocephalus. The diagnosis of tumor was not suspected even at autopsy, until histologic studies were carried out. The aqueduct of Sylvius was obliterated nearly completely by the tumor and accounted for the marked dilatation of the lateral and third ventricles. In retrospect, even with the use of all of our present diagnostic methods, it would seem that it would have been impossible to have arrived at the correct diagnosis in this case since the tumor happened to involve the aqueduct region, at which site inflammatory and other lesions not infrequently result in hydrocephalus.

Case 5: M.G., J.H. No. AA79641. White male, aged 3 weeks. Medulloblastoma of the right cerebral hemisphere near the corpus callosum. Hydrocephalus accompanied by periods of cyanosis and convulsions. Diagnosis unsuspected. Death was sudden.

This infant was born on August 1, 1944, following a difficult instrumental delivery. At birth it was noted that his head was enlarged. Several hours after birth, he had recurrent cyanosis. He apparently improved and was discharged from the hospital on August 10, 1944. During the first six days at home he was well. Following this period, he had several recurrent episodes of

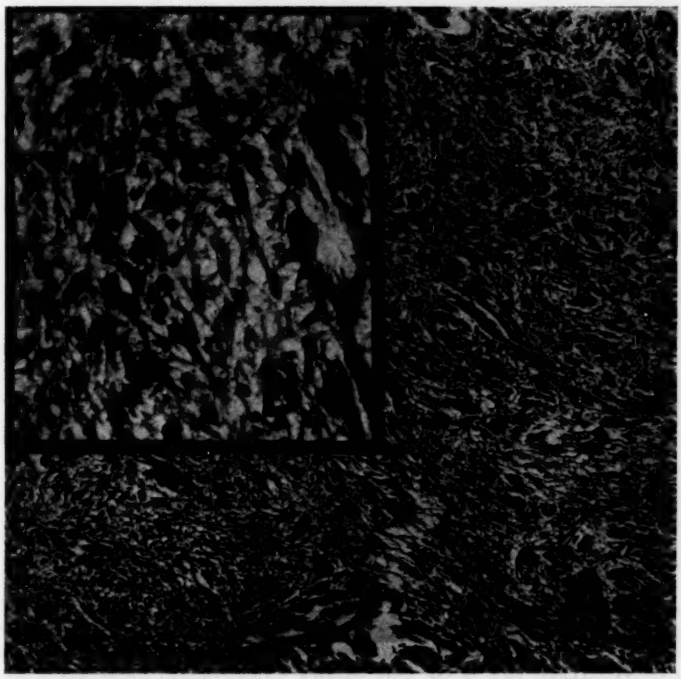

FIG. 5 (Case 4).—Low and high power photomicrographs of an astrocytoma showing spindle and polygonal shaped cells. Under higher power, intracellular fibrils were seen (Hematoxylin and Eosin stain. A:x150. B:x350).

cyanosis and difficulty in respiration. During the two days prior to admission, he had many convulsive seizures with tremors of the arms and legs and rolling and twitching of his eyes. He was admitted to the hospital on August 20, 1944. Since birth his head increased one cm. in circumference.

On admission his head measured 42 cm. in circumference. Both fontanelles were wide and bulging. The infant was alert. He was aware of light and of the presence of people. Other physical findings were normal.

Following admission, there was no change in his general condition. He took his feedings well and had no episodes of cyanosis or convulsions. On the ninth day of hospitalization, he was suddenly found dead in his crib. It was thought that he had hydrocephalus, either on a congenital basis or secondary to intracranial hemorrhage.

A complete necropsy was performed three hours after death. The brain weighed 360 gm. Near the corpus callosum was a large grayish white, moderately firm mass which compressed the right

cerebral hemisphere (Fig. 6). It was poorly demarcated from the surrounding tissue. It obliterated the right ventricle and caused the left ventricle to be shifted markedly to the left.

Preparations from the tumor revealed a fibrillary type of stroma. The fibrils were processes from numerous small astrocytes seen in the tumor. Most of the tumor had diffusely infiltrated the brain and consisted of cells with dark nuclei and barely perceptible cytoplasmic processes (Fig. 7). These were medulloblasts and appeared to enclose many nerve cells and tracts. The tumor was a medulloblastoma.

Comment: This case presents the usual confusing clinical picture of a brain tumor seen in the very young infant. In congenital hydrocephalus, the presence of an enlarged

FIG. 6 (Case 5).—Dorsal view of the brain showing a supratentorial tumor which, on histologic examination, proved to be a medulloblastoma.

head at birth is not unusual. The occurrence of convulsions in association with cyanosis are not infrequently seen in infants and are attributable to cerebral anoxia. However, convulsions are much more common in brain tumors than in congenital hydrocephalus. In reviewing cases of epileptiform convulsions associated with brain tumors, Parker[22] noted their absence in subtentorial tumors. The occurrence of convulsions, particularly of the Jacksonian focal type, would suggest a supratentorial lesion.

This medulloblastoma was supratentorial which is an unusual location for this type of tumor since they nearly always arise in the cerebellum. Honeyman,[23] however, as well as others, has reported cases of cerebral medulloblastoma.

Case 6: J.M.G., J.H. No. 291695. White male, aged 18 months. Medulloblastoma of cerebellum. Course, symptoms, and signs were typical of meningo-encephalitis. Diagnosis not suspected.

This infant was admitted to the hospital on March 31, 1946. He had an upper respiratory

infection for ten days prior to admission. He improved after five days but did not appear to have recovered completely. He remained listless, drowsy and anorexic. He did not respond to surrounding stimuli. For four days prior to admission, he vomited once or twice daily, a few hours after eating. On one occasion the vomiting was projectile. Fever was not present until admission. He had been slow in learning to walk. At the time of admission he walked only with support.

Physical examination revealed a white male infant who appeared to be dull and listless. Temperature was 37.8° C. On occasions he held his head with his hands. Generalized weakness and flabbiness was present. There was loss of subcutaneous tissue. The anterior and posterior fontanelles were closed. The left tympanic membrane was markedly injected. The pupils of the eyes were equal and reacted to light. Photophobia was present. The extraocular movements and eyegrounds were normal. There was slight nuchal rigidity but positive Kernig, Brudzinski and Babinski signs were not elicited. Superficial and deep reflexes were normal.

A lumbar puncture performed on admission revealed clear fluid with normal pressure and no

FIG. 7 (Case 5).—Photomicrograph of a medulloblastoma which consists of small round cells with compact chromatin and scant cytoplasm. Nissl stains revealed chromatin substance within the cytoplasm of some of the tumor cells. Metallic impregnation stains revealed no glial elements (Hematoxylin and Eosin. x75).

cells. The spinal fluid sugar was 86 mg./100 cc. fluid. Therapy was begun with sulfadiazine and parenteral fluids. Two days later the temperature was normal but the infant was still listless and irritable. Nuchal rigidity, marked opisthotonus and positive Brudzinski signs were present. Tuberculin skin test in 0.1 mg. dilution was negative. Lumbar puncture on April 2, 1946 revealed a normal pressure with 146 cells per cmm., type undetermined. The temperature remained normal. On the sixth day of hospitalization, opisthotonus was more marked. Nuchal rigidity and lethargy increased. Projectile vomiting was present. His condition grew worse. Eye examination revealed bilateral nystagmus. The pupils were dilated and did not react to light. The next day, following aspiration of feeding and medication, the infant became cyanotic and respirations ceased. Resuscitation was carried out with suction, artificial respiration, coramine and caffeine. Parenteral feedings were begun. On the eighth day of hospitalization, the infant was found in respiratory failure. Following the use of artificial respiration, coramine, adrenalin and oxygen, diaphragmatic respirations ensued but the infant expired several hours later.

The cultures of the cerebrospinal fluid on both occasions produced no growth. Guinea pig and mouse brain inoculations were normal.

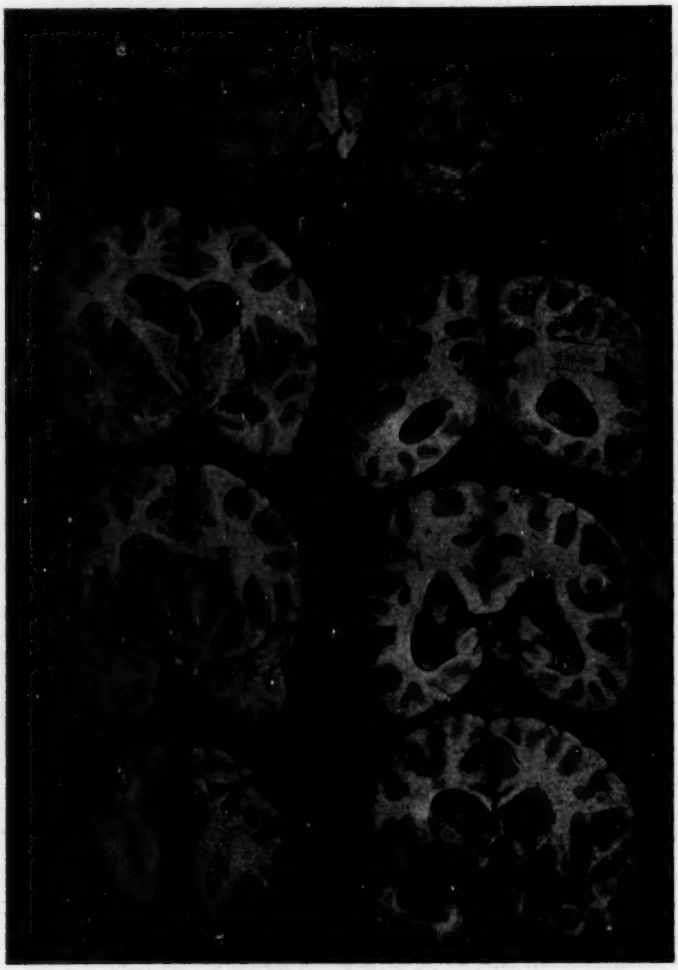

FIG. 8 (Case 6).—Coronal sections of the brain showing hydrocephalus and diffuse infiltration of the cerebellum by tumor tissue. The tumor was a medulloblastoma.

Necropsy was performed ten hours after death. Following incision of the dura, the brain bulged. The brain weighed 1125 gm. The cerebral hemispheres appeared enlarged. The convolutions were broader and the sulci were shallower than usual. A large amount of fluid exuded from the tissue. Uncal and cerebellar herniations were present. The cerebellum was larger and softer than usual. On section, the lateral ventricles were dilated. The usual architecture of the cerebellum was not preserved. It consisted of pinkish white gelatinous-like tissue completely surrounded by a rim of white brain tissue (Fig. 8).

Preparations from the cerebellum revealed large clumps of perivascularly arranged medulloblasts with large vesicular, hyperchromatic nuclei and scant cytoplasm. Intercellular fibrils were present. The cells were arranged in rows. Groups of small astrocytes acted as a stroma for the medulloblasts. The diagnosis of a medulloblastoma was made (Fig. 9).

Comment: The history, physical findings, laboratory data and course were characteristic of meningo-encephalitis. The acute onset with a rapidly progressive course was not typical of a brain tumor. Nystagmus can occur both in encephalitis and cerebellar tumors. The correct diagnosis might have been made if the cells in the spinal fluid had been carefully studied. It was stated on the record that the type of cell was undetermined. This makes one consider the possibility that they were not typical of lymphocytes; and, therefore, might have been circulating medulloblasts. This is the only point which in

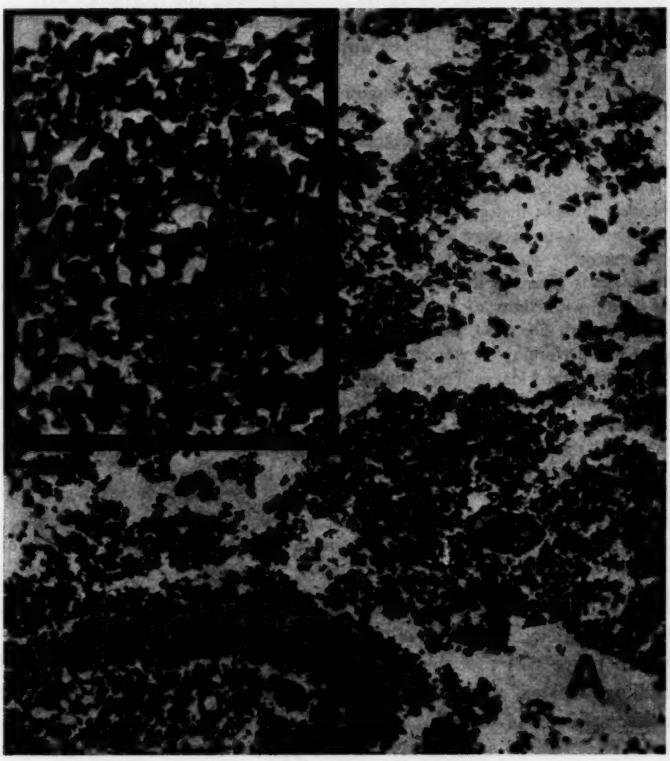

FIG. 9 (Case 6).—Photomicrographs showing low and high power views of a medulloblastoma. Small round cells forming pseudorosettes around blood vessels are seen (Hematoxylin and Eosin stain. A:x150. B:x350).

retrospect might have aided in making the correct diagnosis. The location of the tumor was classical.

Case 7: S.B., J.H. No. 172290. White female, aged 9 months. Tumor of cerebellum (medulloblastoma?). Neurological signs referable to the region of the pons. Intracranial tumor was suspected but not in the correct location. X-ray therapy given.

The infant was admitted to the hospital on July 27, 1934. She apparently had been in good health up to six months of age. At that time she developed a right-sided facial paralysis. It was

thought that she had improved slowly during the following three months. Ten days before admission she became irritable and restless and cried more often than usual. She refused to take her feedings. She had not vomited. Convulsions had not been present. On two occasions during the three months prior to admission, she lapsed into unconsciousness. Each episode lasted about five minutes. Each time she became limp with loss of muscular tone. Immediately following the seizures she appeared to be normal.

Physical examination revealed evidence of recent weight loss. The anterior fontanelle measured 3 x 3 cm. The entire right side of the face including the forehead was immobile while the infant cried. The right eye remained open and its palpebral fissure was wider than that of the left eye. The right corneal reflex was absent. Nystagmus was not present. The eyegrounds were normal. The jaw deviated to the left. There was weakness of the left arm. The abdominal reflexes were absent. All deep reflexes were equal and slightly hyperactive. Ankle clonus, Kernig, Brudzinski and Babinski signs were not elicited.

A ventriculogram was performed on August 9, 1934. There was evidence of poor filling of the inferior horn on the left side and an irregularity of the posterior horn of the left lateral ventricle. During the following days, weakness of the left side of the body became increasingly prominent. Difficulty in swallowing was observed. On August 11, papilledema was noted on the right. The infant became increasingly listless and produced a crowing sound intermittently.

Most observers thought that an intracranial neoplasm was present. The right side of the medulla and the right middle fossa were the two areas which were thought to be the most probable seats of involvement.

X-ray therapy was given on the 20th and 23rd days of hospitalization. On the 22nd day, fever was present along with signs of bronchopneumonia. The infant ran a rapidly downhill course and expired on August 20, 1934, the 25th day of hospitalization.

An autopsy was performed on August 20, 1934. Positive findings included aspiration pneumonia and focal abscesses of the kidneys. The brain weighed 920 gm. The entire cerebellum was edematous. The convolutions were broad and the sulci were compressed. On the outer and upper two-thirds of the right cerebellar hemisphere, there was a lobulated, friable mass which compressed the right peduncle and the right side of the pons. The tumor was attached to the dura mater at the right internal auditory meatus. Upon removal of the brain, a portion of the tumor remained adherent to the dura.

Sections of the tumor were not available for review. According to the records, the tumor consisted of a mixture of large medulloblasts and a considerable number of spongioblasts and astrocytes. A rich network of glia fibers was present.

Comment: The initial onset of a Bell's palsy which was accompanied at a later date by periods of unconsciousness, was suggestive of an intracranial neoplasm. The paralysis of the seventh nerve was probably due to compression of the nerve by tumor at the internal auditory meatus, through which the facial nerve makes exit from the cranial vault. The diagnosis was suspected.

This tumor was treated with X-ray. At the present time, this is not considered the treatment of choice. Ingraham and Campbell[24] emphasized the dangers of such therapy without previous biopsy. Inasmuch as some tumors are amenable to operative removal and cure, X-ray therapy in such cases could do only harm.

The recorded description of the tumor, the location and the dural invasion point to the likelihood that this was a medulloblastoma.

The various features of each case are tabulated in Table II.

Summary

Seven cases of brain tumors occurring in infants are presented. Six occurred in males and one was in a female. Three of them arose in the cerebellum while the other four were supratentorial. The tumors included two medulloblastomas, one spongio-

TABLE II

Case	1	2	3	4	5	6	7
Age	22 mo.	22 mo.	21 mo.	4 mo.	3 wk.	18 mo.	9 mo.
Sex	Male	Male	Male	Male	Male	Male	Female
Type of Tumor	Hemangio-blastoma	Ependy-mona	Spongio-blastoma Polare	Astrocytoma	Medullo-blastoma	Medullo-blastoma	Medullo-blastoma?
Location	Right cere-bral hemi-sphere	Cerebellum	Brain Stem	Midbrain	Near corpus callosum	Cerebellum	Cerebellum
Diagnosis Suspected	Yes	Yes	No	No	No	No	Yes
Inaugural Symptoms and Signs	Paresis of left extremities	Recurrent vomiting	Retarded speech; fell to floor while walking; somnolence; anorexia	Enlargement of head	Hydroceph-alus; cyanosis	Retarded walking; drowsiness; fever	Syncope; Bell's palsy
Vomiting	No	Yes	O*	O*	O*	Yes	No
Convulsions	No	O*	O*	No	Yes	O*	No
Papilledema	Yes	Yes	O*	O*	O*	No	Yes
Enlargement of head	No	O*	O*	Yes	Yes	O*	O*
Duration of clinical course before opera-tion or exitus	2 wk.	5 mo.	1 month (possibly 1 year)	4 mo.	3 wk.	3 wk.	3 mo.
Course	Removal of tumor; living and well	Death follow-ing surgery	Expired	Expired following surgery	Expired	Expired	Expired
Clinical Impression	Tumor of right cerebral hemisphere	Midline cerebellar tumor	Hydroceph-alus; cerebral agenesis; cerebral sclerosis; Schilder's disease	Congenital hydrocephalus	Hydroceph-alus; possible intracranial hemorrhage	Encephalitis	Tumor of medulla; tumor of middle fossa

* Not recorded in chart.

blastoma polare, one ependymoma, one astrocytoma and one hemangioblastoma. The seventh case probably was also one of medulloblastoma. One of the proven medullo-blastomas was supratentorial, which is unusual so far as location is concerned. The hemangioblastoma arose in the cerebrum. The location of this tumor is also a rare one and to my knowledge, it is the first case of its type reported in an infant in whom full recovery occurred following removal of the tumor.

The diagnosis was unsuspected in four cases. Three of these infants were believed to be suffering from congenital hydrocephalus while the fourth was thought to be afflicted with encephalitis. The ways in which the correct diagnosis might have been made are discussed. Since bizarre clinical patterns are sometimes produced by brain tumors in

infants and the diagnosis frequently overlooked, the possibility should be kept in mind by the pediatrician in considering the differential diagnosis of conditions producing signs referable to the nervous system.

ACKNOWLEDGEMENTS

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REFERENCES

1. Bailey, P., Buchanan, D. H., and Bucy, P. C., Intracranial Tumors of Infancy and Childhood, Univ. of Chicago Press, Chicago, 1939.
2. Globus, J. H., Zucker, J. M., and Rubinstein, J. M., Tumors of brain in children and adolescents, Am. J. Dis. Child. **65**:604, 1943.
3. Cushing, H., Intracranial tumors of preadolescence, Am. J. Dis. Child. **33**:551, 1927.
4. Stern, R. O., Cerebral tumors in children, Arch. Dis. Childhood **12**:291, 1937.
5. Bailey, P., Tumors of the nervous system, Brenneman's Practice of Pediatrics, Vol. IV, W. F. Prior Co., Hagerstown, Md.
6. Gross, S. W., Tumors of the brain in infancy, Am. J. Dis. Child. **48**:739, 1934.
7. Habel, K., Brain tumors from pediatrician's viewpoint, J. Pediat. **10**:502, 1937.
8. Russell, D. S. and Ellis, R. W. B., Circumscribed cerebral tumors in young infants, Arch. Dis. Childhood **8**:329, 1933.
9. Rand, C. W., and Van Wagenen, R. J., Brain tumors in childhood, J. Pediat. **6**:322, 1935.
10. Wollstein, Martha, and Bartlett, F. H., Brain tumors in young children, Am. J. Dis. Child. **25**:257, 1923.
11. Critchley, M., Diagnosis of cerebellar tumors in children, Brit. J. Child. Dis. **23**:165, 1926.
12. Marburg, O., Some remarks on tumors of brain in childhood, J. Nerv. & Ment. Dis. **95**:446, 1942.
13. Bailey, P., and Cushing, H., Medulloblastoma cerebelli, Arch. Neurol. & Psychiat. **14**:192, 1925.
14. Walt, F., Medulloblastoma in infant with abnormal cells in cerebrospinal fluid, Arch. Dis. Childhood **14**:84, 1939.
15. Elsberg, C. A., and Globus, J. H., Tumors of brain with acute onset and rapidly progressive course, Arch. Neurol. & Psychiat. **21**:1044, 1929.
16. Merritt, H. H., Cerebrospinal fluid in cases of tumors of the brain, Arch. Neurol. & Psychiat. **34**:1175, 1935.
17. Bailey, P., Cushing, H., and Eisenhardt, L., Angioblastic meningiomas, Arch. Path. **6**:953, 1928.
18. Sachs, E., The Diagnosis and Treatment of Brain Tumors, C. V. Mosby, St. Louis, 1931.
19. Fincher, E. F., Jr., and Coon, G. P., Ependymomas, Arch. Neurol. & Psychiat. **22**:19, 1929.
20. Strauss, I., and Globus, J. H., Tumor of the brain with disturbance in temperature regulation, Arch. Neurol. & Psychiat. **25**:506, 1931.
21. Bailey, P., and Eisenhardt, L., Spongioblastomas of the brain, J. Comp. Neurol. **56**:391, 1932.
22. Parker, H. L., Epileptiform convulsions; incidences of attacks in cases of intracranial tumor, Arch. Neurol. & Psychiat. **23**:1032, 1930.
23. Honeyman, W. M., Cerebral medulloblastoma, Am. J. Path. **13**:1003, 1937.
24. Ingraham, F. D., and Campbell, J. B., Dangers of radiation without biopsy of brain tumors in children, New England J. Med. **224**:925, 1941.
25. Friedman, J. J., and Solomon, C. I., Tumors of choroid plexus in childhood, Am. J. Dis. Child. **52**:114, 1936.

SPANISH ABSTRACT

Desde que algunas raras observaciones de tumores cerebrales en el lactante han sido presentados y teniendo en cuenta que los signos y sintomas en esta epoca de la vida varian considerablemente de los observados en niños mayores y adultos, el diagnostico de estas lesiones es relativamente frecuente.

No parece haber una gran predileccion de estros tumores en los primeros tiempos de la vida por las regiones infratentoriales en mayor frecuencia que por las regiones supratentoriales.

Los gliomas comprenden la mayor parte de las observaciones de estos tumores.

Siete casos de tumores cerebrales en el lactante son presentados. Seis comprenden niños varones y uno a hembra; tres de ellos asientan en el cerebelo y los otros cuatro fueron supratentoriales.

Los tumores incluyen: dos meduloblastomas, un espongioblastoma polar, un ependimoma, un astrocitoma y hemoangioblastoma, el septimo caso fue tambien probablemente un meduloblastoma. Uno de los probables meduloblastomas fue supratentorial, lo cual es poco frecuente en cuanto a localizacion se refiere. El hemoangioblastoma se desarrollo en el cerebro. La localizacion de este tumor es tambien rara, pensando que es el primer caso de este tipo reportado en un lactante, cuyo total restablecimiento se obtuvo despues de la extirpacion del tumor.

El diagnostico paso desapercibido en cuatro casos, tres de los niños fueron diagnosticados de hidrocefalia congenita y en el cuarto se penso que se trataba de una encefalitis.

La manera de como puede hacerse el diagnostico correcto es ampliamente informada.

555 *Prospect Pl.*

KAPOSI'S VARICELLIFORM ERUPTION; A PRIMARY INFECTION WITH HERPES SIMPLEX VIRUS

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KAPOSI[1] described a syndrome in which children developed an eruption and a febrile reaction as a complication of a preexisting eczema. The eruption appears on the areas of the old eczema and occasionally invades the neighboring healthy skin. It evolves through various stages of vesiculation, umbilication, rupture and desiccation. The lesions appear in recurrent crops for many days and, when they finally heal, only the signs of the original eczema persist. The etiology of Kaposi's varicelliform eruption was in doubt until it was found recently that the virus of herpes simplex could be recovered from the acute skin lesions.[2-5] The syndrome was shown to occur not only in children but also in adults.[6-10] The development of herpes neutralizing antibodies in the blood during convalescence led to the assumption that the acute eruption was the result of primary infection with the virus. Vaccine virus can also invade the eczematized cutaneous lesions and cause a similar disease condition, eczema vaccinatum.[11-15] Clinically, Kaposi's eruption and eczema vaccinatum are in many respects alike and laboratory procedures are required in order to establish the diagnosis. Four cases of Kaposi's varicelliform eruption were recently reported in which diagnosis was established by recovery of virus of herpes simplex from cutaneous lesions.[6] This second report deals with five additional cases. In three of them the herpes simplex virus could be isolated, and in two in which isolation was not successful the antibody titer against herpes rose during convalescence.

CASE REPORTS

R.E., a 20-month-old white boy, had had infantile eczema since the age of three months and had never been vaccinated. He developed an acute illness characterized by fever, lymphadenitis and a vesicular dermatitis superimposed on the eczema. The acute lesions cleared in about two weeks. Swabs of the cutaneous lesions taken two days after the onset of the illness and again five days later were inoculated onto the scarified corneas of rabbits. Herpetic keratitis developed in both rabbits. Nine days before the patient's admission his mother had had "fever blisters."

C.F., a 13-month-old white girl, had had atopic dermatitis since three weeks of age and had not been vaccinated. On admission there was fever, lymphadenitis and a few scattered vesicles on the face, neck and ears. The acute lesions remained scanty and the patient was not very ill. A swab of the vesicular lesions taken on the fourth day after the onset of the eruption produced herpetic lesions on the scarified cornea of a rabbit. Both parents had had recurrent herpes and the mother had labial herpes three days after the patient's admission.

G.N., a 22-year-old white man with neurodermatitis, exhibited an acute vesicular eruption on the face, neck and dorsum of the right hand. Herpetic lesions were also present on the lips, in the mouth and on the hard palate. The acute skin lesions healed in a few days. A swab of the skin lesions taken on the fifth day after the onset produced herpetic keratoconjunctivitis on both corneas of a rabbit. About three days before the acute episode the patient had kissed his mother who had "cold sores" on the lip.

W.S., a 26-year-old white man with atopic dermatitis of long standing developed a generalized vesicular eruption. Although no virus was recovered from a swab of the skin lesions taken seven

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days after the onset, the patient showed an antibody increase against herpes during convalescence. The patient recovered and was discharged after two weeks. He had been exposed to the virus of herpes simplex when his 2-year-old baby developed primary herpetic gingivostomatitis about a week before the onset of his vesicular eruption.

M.N., a 2-year-old white boy with a history of eczema developed an acute eruption on the face, right arm and leg. Swabs of the dried skin lesions taken eight days after the onset failed to yield a virus. Antibodies against herpes developed during convalescence. The patient had not been vaccinated and had been exposed to three members of the immediate family, all of whom had herpes.

Laboratory Data

Isolation of strains of virus: The contents of several relatively fresh vesicles on the patient's skin were taken up on a cotton swab previously moistened with sterile saline,

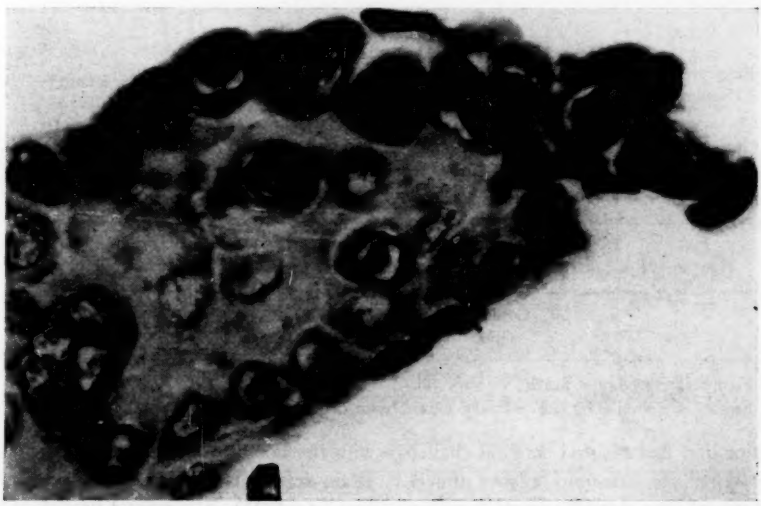

Fig. 1. Kaposi's varicelliform eruption (case C.E.). Intranuclear inclusions in rabbits cornea. Hematoxylin and eosin. x1400.

and the material used to rub onto the scarified corneas of a rabbit.* When keratoconjunctivitis developed in two or three days, the cornea and nictitating membrane were removed.* A piece of the cornea was removed for histologic section. The nictitating membrane and the remainder of the cornea were pooled and ground in a mortar with 2 cc. of saline, and the suspension centrifuged at 1500 rpm for a few minutes. The supernatant fluid was then injected intracerebrally into mice.* From the mice that became ill the brains were removed aseptically and ground in a mortar with alundum and saline. After centrifugation the supernatant fluid was injected intracerebrally into other mice. After several passages infected brains were placed in "lusteroid" tubes and stored in dry ice. Tissues and tissue suspensions were routinely cultured on blood agar plates and found to be sterile.

Identity of the strains of herpes simplex: The agent recovered from the cutaneous lesions was identified as a strain of herpes virus by the demonstration of eosinophilic

* All operations were performed while animals were under full ether anesthesia.

intranuclear inclusions of the herpetic type in the corneas of rabbits (Fig. 1) and by the demonstration of cross-immunity with a known strain of herpes (H.F. strain) in mice and rabbits. Freshly prepared 10% mouse brain suspensions from infected animals were employed to test immunity. Rabbits that had recovered from infection with human material were tested for ocular immunity. The results are shown in Table I. Rabbits that had received one of the R.E., C.F., or G.N. strains of virus were resistant to the H.F. strain. The normal control animals developed keratoconjunctivitis and succumbed to encephalitis in seven to nine days.

TABLE I

OCULAR RESISTANCE OF RECOVERED RABBITS TO THE H.F. STRAIN OF HERPES SIMPLEX

Experiment Number	Rabbit's cornea had previously received		Result*
	Strain	Number of Rabbits	
1	Controls R.E.	2 3	8, 8 S, S, S
2	Controls C.F.	2 1	8, 9 S
3	Controls G.N.	1 2	7 S, S

* Figure signifies day of death; S=Survival.
Freshly prepared 10% H.F.-infected mouse brain suspensions used to test the above rabbits.

Mice that had resisted cerebral challenge with the homologous human strain of virus were tested for immunity against the H.F. strain several weeks later. All were solidly immune whereas normal control mice succumbed (Table II). The reverse procedure gave similar results: H.F.-immune mice were resistant to infection with the R.E., C.F. or G.N. strains of virus (Table III).

Neutralization tests: Neutralization tests were performed with the patient's sera in order to establish a relationship between the recovered agent and the disease. Sera were obtained during the acute phase of the illness and at least three weeks later during the convalescent period. They were stored in dry ice until used for the neutralization tests. Twenty per cent suspensions of infected mouse brain were freshly prepared. Decimal dilutions were made in rabbit serum-saline* giving concentrations of 1:5, 1:50, . . . etc., up to 1:500,000. These, when added to equal amounts (0.2 cc.) of undiluted test sera, gave final concentrations of 1:10, 1:100 . . . etc., up to 1:1,000,000. The mixtures of virus dilution and serum were incubated in a water bath for two hours at 37°C. At the end of this time the mixtures were injected intracerebrally into groups of four mice each. The mice were observed for a period of three weeks. They were watched daily for signs of central nervous system involvement, and the number of deaths were recorded. LD_{50} titers were calculated according to the method of Reed and Muench[16] and neutralization

* Rabbit serum-saline consisted of rabbit serum which had been inactivated at 56° for one-half hour and made up to 10% in saline.

indexes determined by the method described in "Laboratory Methods of the United States Army."[17] The serum of a normal rabbit was used as a control.

Table IV is a protocol of a neutralization test on the serum of R.E. in which a homologous strain of virus was employed. It can be seen that the acute phase serum showed a

TABLE II

CEREBRAL RESISTANCE OF IMMUNIZED MICE TO THE H.F. STRAIN OF HERPES SIMPLEX

Experiment number	Mice had last received		Results*
	Strain	Route	
1	Controls	—	6/6
	R.E.	Intracerebral	0/6
2	Controls	—	8/8
	C.F.	Intracerebral	0/5
3	Controls	—	6/6
	G.N.	Intracerebral	0/6

* Numerator = mice that died; denominator = mice inoculated.
Freshly prepared 10% H.F.-infected mouse brain suspensions used to test the above mice.

TABLE III

CEREBRAL RESISTANCE OF H.F. IMMUNIZED MICE TO HUMAN STRAINS OF HERPES SIMPLEX

Experiment Number	Strain of Herpes*	Group of Mice	Result**
1	R.E.	Controls	4/4
		H.F. Immune	0/4
2	C.F.	Controls	5/5
		H.F. Immune	0/6
3	G.N.	Controls	4/4
		H.F. Immune	0/4

* Freshly prepared 10% infected mouse brain suspensions used to test the above mice.
** Numerator = mice that died; denominator = mice inoculated.
Note: In the above experiments the H.F. immune mice had survived a previous cerebral challenge with the H.F. strain.

neutralization index of 6, little above the control, which increased to 1300 in the convalescent phase serum: a 200-fold increase. This result is included in Table V in which are listed the results of all the tests with the acute and convalescent phase sera of the 5 patients. Three of the patients (R.E., C.F. and G.N.) from whose skin lesions an agent was recovered showed a neutralization index little above that of the control during

TABLE IV

NEUTRALIZATION TEST WITH R. E. SERA AGAINST THE HOMOLOGOUS R.E. STRAIN OF VIRUS
Neutralization test (intracerebral method) in mice
Serum virus mixtures at 37°C. for two hours

Serum in Mixture	Dilution of R.E. virus in mixture					LD_{50} titer	Neut. index*	Index increase
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}			
								fold
Normal rabbit	—	4/4**	4/4	3/4	0/4	4.3	—	—
R.E. acute 7-22-46	—	4/4	1/4	2/3	1/4	3.5	6	—
R.E. conval. 8-29-46	2/4	0/4	1/4	0/4	—	1.2	1300	200

* Neutralization index $= \frac{LD_{50} \text{ titer normal rabbit serum}}{LD_{50} \text{ titer test serum}}$.

** Numerator = mice that died; denominator = mice inoculated.

TABLE V

NEUTRALIZATION TESTS WITH PATIENT'S SERA AND STRAINS OF HERPES SIMPLEX

Serum in mixture	Homologous test			Heterologous test		
	LD_{50} titer	Neut. index	Convalescent index increase	LD_{50} titer	Neut. index	Convalescent index increase
			fold			fold
Normal rabbit	4.3	—	—	5.2*	—	—
R.E. acute	3.5	6	—	4.5	5	—
R.E. conval.	1.2	1300	200	3.5	50	10
Normal rabbit	2.7	—	—	4.7*	—	—
C.F. acute	1.8	8	—	—	—	—
C.F. conval.	0.7^-	100^+	13^+	2.5	160	—
Normal rabbit	3.0	—	—	5.2*	—	—
G.N. acute	1.5	32	—	4.0	16	—
G.N. conval.	0.5^-	320^+	10^+	3.0	160	10
Normal rabbit	—	—	—	4.8**	—	—
W.S. acute	—	—	—	3.2	40	—
W.S. conval.	—	—	—	2.0	630	15
Normal rabbit	—	—	—	4.3**	—	—
M.N. acute	—	—	—	4.3	1	—
M.N. conval.	—	—	—	2.3	100	100

* H.F. strain of virus used in this test.
** C.E. strain of virus used in this test.

the acute phase and an increase during convalescence. Two of the three (R.E. and G.N.) also showed an increase when the heterologous H.F. strain was used. No acute phase serum was available for the test with the heterologous H.F. strain with the third patient (C.F.), but antibodies were present in the convalescent phase serum. An agent was not obtained from the cutaneous lesions of the two remaining patients (W.S. and M.N.); so that only tests with the heterologous C.E. strain of virus were performed. Patient W.S.

TABLE VI

VIRUS AND ANTIBODY STUDIES ON CASES OF KAPOSI'S VARICELLIFORM ERUPTION

	Patient	Age	Date exposed	Incubation period	Virus recovered	Remarks on antibodies
Previously reported (6)	J.M.	14 mo.	11-20-45 (mother)	days 5–6	11-29-45	Antibody increase during convalescence
	F.R.	16 yr.	12-22-45 (father)	8–10	1- 5-46	Antibody increase during convalescence
	E. B.	25 yr.	2-6-46 (boy friend)	5–7	2-14-46	Antibodies present in acute serum. No increase during convalescence
	H.T.	23 yr.	4-15-46 (boy friend)	10	4-26-46 5- 2-46	Fatal case: no antibodies in acute serum.
Present report	R.E.	20 mo.	7-11-46 (mother)	9	7-22-46 7-27-46	Antibody increase during convalescence
	C.F.	13 mo.	past few days (mother)	several	10-18-46	Antibody increase during convalescence
	G.N.	22 yr.	2-14-47 (mother)	3–5	2-21-47	Antibody increase during convalescence
	W.S.	26 yr.	5-20-47 (son)	10	—*	Antibody increase during convalescence
	M.N.	2 yr.	8-8-47 (brother)	8	—*	Antibody increase during convalescence

* Unsuccessful attempts to recover an agent.

exhibited little antibody in the acute phase serum and a 15-fold increase during convalescence and patient M.N. a 100-fold increase.

The combined data on the five cases reported here and four other cases previously reported are listed in Table VI. Four of the patients were children 13 months to two years of age, and five were adults 16 to 26 years of age. All had been exposed to the virus of herpes simplex. Incubation periods were estimated to be between three and ten days. The virus was recovered from seven of the patients within two to seven days of hospitalization. On two occasions it was recovered a second time from the skin lesions

after five or six days. Two patients were examined late in the disease; their skin lesions failed to yield a virus. Seven patients developed antibodies against herpes after recovery. One patient had antibodies in the acute phase of the illness but no rise occurred during convalescence. As the remaining patient died, serum was obtained only in the acute period and no antibody was found.

Discussion

The virus of herpes simplex is found widely disseminated in the population. Infection commonly takes place in childhood, usually causing an acute stomatitis[18] accompanied by generalized systemic manifestations. Neutralizing antibodies develop after recovery.[19,20] The patients are usually immune to reinfection but suffer from localized, recurrent "fever blisters" or "cold sores." Apparently in some individuals neutralizing antibodies develop on the basis of an inapparent infection. Primary invasion of the body by the virus of herpes simplex may also take the form of an encephalitis,[21,22] meningitis[23] or vulvovaginitis.[24] Whether Kaposi's varicelliform eruption is a primary infection with the virus of herpes simplex is uncertain as yet. Previous reports indicate[4-6] that this may be the case. The cases reported here lend additional evidence to the view that one deals with a primary infection.

Summary

Five cases of Kaposi's varicelliform eruption are reported of which three were children and two were adults. The patients had been exposed to one or more members of the immediate family who had herpes simplex infection. The virus of herpes simplex was recovered from two children and one adult. In all five cases the neutralization index of their sera against herpes virus, little higher than that of control serum during the acute phase of their illness, rose during convalescence. Corroborative evidence is obtained from a study of the above cases that Kaposi's varicelliform eruption is in all probability a manifestation of primary infection with herpes simplex virus in persons with eczema.

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References

1. Kaposi, M., Pathology and Treatment of Diseases of Skin for Practitioners and Students, Wm. Wood and Company, New York, 1895, p. 346.
2. Seidenberg, S., Zür Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. u. Bakt., **4**:398, 1941.
3. Wenner, H. A., Complications of infantile eczema caused by virus of herpes simplex, Am. J. Dis. Child. **67**:247, 1944.
4. Blattner, R. J., Heys, F. M., and Harrison, M. L. K., Etiology of Kaposi's varicelliform eruption, J. Pediat. **27**:207, 1945.
5. Jaquette, W. A., Jr., Convey, J. H., and Pillsbury, D. M., Kaposi's varicelliform eruption: studies on etiology, Am. J. Dis. Child. **71**:45, 1946.
6. Ruchman, I., Welsh, A. L., and Dodd, K., Kaposi's varicelliform eruption: isolation of virus of herpes simplex from cutaneous lesions of three adults and one infant, Arch. Dermat. & Syph. **56**:846, 1947.

7. Barton, R. L., and Brunsting, L. A., Kaposi's varicelliform eruption, Arch. Dermat. & Syph. **50**:99, 1944.
8. Lynch, F. W., Evans, C. A., Bolin, V. S., and Steves, R. J., Kaposi's varicelliform eruption: extensive herpes simplex as a complication of eczema, Arch. Dermat. & Syph. **51**:129, 1945.
9. Lynch, F. W., and Steves, R. J., Kaposi's varicelliform eruption, Arch. Dermat. & Syph. **55**:327, 1947.
10. Barker, L. P., and Hallinger, E. S., Systemic herpes simplex (Kaposi's varicelliform eruption), J.A.M.A. **135**:149, 1947.
11. Hershey, F. B., and Smith, W. E., Generalized vaccinia in an eczematous child, Am. J. Dis. Child. **69**:33, 1945.
12. Freund, H., Zur Ätiologie der Pustulosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52, 1934.
13. Pepple, A. W., Murrell, T. W., and Fowlkes, R. W., Varicelliform eruption of Kaposi, South. M.J. **35**:667, 1942.
14. Ellis, F. A., Eczema vaccinatum: its relation to generalized vaccinia, J.A.M.A. **104**:1891, 1935.
15. Rubenstein, A. D., Eczema vaccinatum, New England J. Med. **237**:395, 1947.
16. Reed, L. J., and Muench, H., Simple method of estimating 50 per cent end-points, Am. J. Hyg. **27**:493, 1938.
17. Simmons, J. S., and Gentzkow, C. J., Laboratory Methods of the United States Army, Lea and Febiger, Philadelphia, 1944, p. 591.
18. Dodd, K., Johnston, L. M., and Buddingh, G. J., Herpetic stomatitis, J. Pediat. **12**:95, 1938.
19. Burnet, F. M., and Williams, S. W., Herpes simplex, M. J. Australia **1**:637, 1939.
20. Scott, T. F. M., Steigman, A. J., and Convey, J. H., Acute infectious gingivostomatitis; etiology, epidemiology and clinical picture of common disorder caused by virus of herpes simplex, J.A.M.A. **117**:999, 1941.
21. Smith, M. G., Lennette, E. H., and Reames, H. R., Isolation of virus of herpes simplex and demonstration of intranuclear inclusions in case of acute encephalitis, Am. J. Path. **17**:55, 1941.
22. Zarafonetis, C. J. D., Smadel, J. E., Adams, J. W., and Haymaker, W., Fatal herpes simplex encephalitis in man, Am. J. Path. **20**:429, 1944.
23. Armstrong, C., Herpes simplex virus recovered from spinal fluid of suspected case of lymphocytic choriomeningitis, Pub. Health Rep. **58**:16, 1943.
24. Slavin, H. B., and Gavett, Elizabeth, Primary herpetic vulvovaginitis, Proc. Soc. Exper. Biol. & Med. **63**:343, 1946.

SPANISH ABSTRACT

Erupcion Varioliforme de Kaposi, su Relacion con el Virus del Herpe Simple

Se aportan nuevas pruebas en favor del punto de vista que sostiene que la erupcion varioliforme de Kaposi, puede ser producida por la infeccion del virus del herpe simple, en personas con dermatitis atopica.

Tres niños y dos adultos desarrollaron este sindrome. Todos ellos habian tenido contacto con uno o mas miembros de la familia que tenian herpe simple. El mismo virus fue identificado en las lesiones agudas cutaneas de dos de los niños y un adulto. La presencia de eosinofilos, cuerpos intracelulares incluidos en la lesion de la cornea del conejo y la demostracion de inmunidad cruzada en animales, con la cepa H.F. de herpes establece la identidad de los agentes recogidos. En todos los cinco casos el indice de neutralizacion del suero frente al virus del herpe ligeramente mas alto que el del suero control durante la fase aguda de la enfermedad aumento durante la convalecencia. Estos cinco casos vienen a añadir nueva corroboracion a las evidencias ya acumuladas que el eritema varioliforme de Kaposi puede ser una manifestacion de ataque primaria de herpe simple en personas con eccema.

La comprobacion del virus y la demostracion de los anticuerpos producido durante la convalecencia distinguen esta enfermedad del eccema vaccinal el cual es debido a la infeccion con virus vaccinal en personas con dermatitis atopica.

Elland and Bethesda Aves.

BAL IN THE TREATMENT OF ARSENIC INGESTION OF CHILDREN

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THE advantages of a therapeutic agent capable of counteracting the effects of a toxic substance which has passed the intestinal barrier are obvious. BAL (dimercaprol[1] or 2,3-dimercaptopropanol) is such an antidote for arsenic poisoning. Early developments as to the nature and uses of this substance were retained in military secrecy during the past war.[2] Since its recent release, a potentially wide range of applications[3-8] has been found. Its value, mode of action, and side effects in arsenic poisoning of experimental animals and adults have been carefully studied.[9-21] No reports concerned particularly with its uses in children have appeared heretofore.

The ingestion of substances containing arsenic is a frequent cause of poisoning in infants and children. At the Charity Hospital during the past ten years, it ranked second among causes for admission and fifth among causes of death due to accidental poisoning. Syrup insecticides are commonly as attractive to young children as they are for insects.

Even when the amount of ingested arsenic can be determined, there may be doubt as to the effect based on an uncertain range of tolerance of the child. A lethal outcome can occur with as little arsenic as 1.0 mg./kg. body weight.[20] As with most arsenicals, furthermore, symptoms may be delayed so that initial well-being of the child may be misleading. Because of this an antidote, effective as well as innocuous, which could be justifiably administered upon the suspicion of poisoning would be desirable.

The efficacy of BAL in treatment of arsenic poisoning has been definitely established. Therapeutic and toxic doses for adults, as well as the reactions and side effects from such doses, have been reported by several groups of investigators; properly administered, it is evidently innocuous for adults.[10-15] The purpose of this paper is to review the experiences with the use of this drug for 42 children who had ingested arsenic, particularly to determine the frequency, severity, and types of reactions it causes and to ascertain if criteria for safety are met in such patients.

BAL is a dithiol compound which competes with the tissues for arsenic.[9,11,17] In experimentally poisoned animals arsenic becomes fixed to the SH radicals of the tissue thiols within the cells. The enzyme actions of these thiols are blocked by combination with arsenic so that cellular metabolism is compromised and cell death follows. BAL possesses free SH radicals, and arsenic has a greater affinity for these than it does for those of the tissue thiols. This competitive attraction is so great that even arsenic already combined in the cells will yield to unite with BAL. The BAL-thioarsenate combination thus formed is non-toxic and is excreted by the kidney. Despite this selective affinity, however, BAL must be administered before cellular damage becomes irreversible.

BAL was given to 42 infants and children who were all known to have ingested substances containing arsenic; 22 had taken potentially lethal amounts. They ranged in age

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from 6 months to 10 years, but 86% of them were between 1 and 4 years. At admission, 82% of them were vomiting, 43% were retching, 12% had diarrhea, 9% had evident abdominal pain, and 9% were prostrated. A similar group of 111 such patients was admitted and treated by conventional methods prior to the time that BAL became available to us. Three of these died. For those who lived, the average duration of hospitalization was 4.2 days, and almost 30% of them had definite evidences of arsenic poison-

TABLE I

COMPARISON OF PATIENTS

	Total number of of patients	Deaths	Average hospital stay, days	Symptoms of poisoning, per cent	
				when admitted	12 hrs. later
Without BAL	111	3	4.2	46.2%	29.3%
With BAL	42	0	1.6	47.6%	0%

TABLE II

REACTIONS IN 42 PATIENTS, RELATED TO DOSAGE

Reactions	Dosage of BAL, mg./kg. body weight			
	2.0–2.9	3.0–4.9	5.0–40.5	Total
Anorexia	1	5	6	12
Restlessness	1	1	7	9
Vomiting	0	1	4	5
Pain at injection site	1	2	2	5
Salivation	1	2	2	5
Hypertension	1	3	5	9
Fever	0	4	4	8
Tachycardia	0	2	5	7
Convulsions	0	0	3	3
"Leukotoxic" effect	1	1	4	6
Reducing substance in the urine	0	0	4	4
Patients with reactions	3	10	12	25
Total number of patients	15	15	12	42

ing lasting beyond twelve hours. By comparison (Table I), there were no deaths among the 42 patients more recently treated, the average hospital stay was 1.6 days and none of the symptoms noted above persisted after twelve hours.

Reactions attributed to BAL are of interest; in Table II these are related to dosage schedules. With less than 3.0 mg./kg. body weight, one-fifth of the children had mild subjective reactions (irritability, restlessness, and anorexia), which could easily have been overlooked. In the range from 3.0 to 4.9 mg./kg. two-thirds of the children had such reactions; while these were more pronounced and occasionally accompanied by fever, they were never alarming. All children who had more than 5.0 mg./kg. experi-

enced reactions, the severity of which depended on the size of the individual doses. Up to 10.0 mg./kg. more definite irritability and restlessness were frequently accompanied by tachycardia, hypertension, fever, and the presence of reducing substances in the urine. In doses of 25.0 or more mg./kg. reactions were alarming; after from ten to ninety minutes the blood pressure of all 3 patients who received such doses rose suddenly 30 to 50 mm.Hg. Such elevations were followed by convulsions and coma. The resemblance of these episodes to those of hypertensive encephalopathy in nephritis was striking. The several reactions encountered with average, large, and excessive doses of BAL are illustrated in the following brief protocols:

1. A 21-month old girl ate a full ounce of ant syrup containing 8.2% arsenic. When this was discovered, salt water and milk were given, and she vomited five times before arriving at the hospital an hour later. In the emergency room her stomach was lavaged, and she was dismissed. She continued to vomit and retch, however, so was brought back to the hospital five hours later. By that time she had colicky abdominal pain, and had passed five liquid stools. When admitted, she was given 2.5 mg. BAL/kg. intramuscularly. This was repeated every six hours for ten doses. Urinalysis was negative. After the second injection retching, abdominal pain, and diarrhea ceased. No other therapy was given except an infusion of dextrose in normal saline for moderate dehydration. The only reaction which could conceivably be attributed to BAL was anorexia, which lasted until BAL was discontinued.

2. An 11-month old girl ingested an unknown amount of a red liquid ant poison. She was given no antidote, but vomited three times before arriving at the hospital. Just before and after admission she had two loose watery stools containing flecks of blood. Treatment with BAL was begun six hours after poisoning. She was given 5.0 mg./kg. every four hours for four doses and once daily thereafter for three days. Moderate restlessness followed each of the first four injections; tenderness and induration after one of these lasted for eight hours. A half-hour after the second and third doses the pulse rate increased 30 to 40 beats from the resting level. After the fourth dose the rectal temperature ranged from 38.8°C. to 40°C. until six hours after the final injection.

3. A 24-month old girl ate an unknown amount of ant syrup known to contain 1% arsenic. Ten minutes later she vomited, and was given milk. She vomited and retched continually on the way to the hospital. In the emergency room magnesium oxide and ferric chloride were instilled after gastric lavage. She was admitted four hours after ingesting the poison. Through an error in calculation she received 25.0 mg. BAL/kg. This was repeated four hours later. About 30 minutes after the first injection anorexia, vomiting, and extreme restlessness were noted, but these subsided within an hour. A similar reaction occurred ten minutes after the second injection. At that time cutaneous flushing was noted. The temperature was 38.3°C., the pulse rate had increased to 146/min., and by 90 minutes the blood pressure had arisen from a resting level of 90/60 to 140/90 mm.Hg. There ensued a moderately severe, generalized convulsion, which lasted three minutes; this was followed by coma and stupor for the next hour, after which she appeared well. There was no change in the total leukocyte count, but six hours after the second dose of BAL polymorphonuclear cells had dropped from 75% to 38%. After discontinuing the drug the proportion of polymorphonuclear cells slowly increased to 51% within three days. No reducing substances were present in the urine. Following the convulsion, a continuous infusion of 5% dextrose in distilled water was given in the hope of hastening the elimination of excess BAL.

Table III compares our observations with those reported by two groups[14,15] working with adults. In this table we have combined adult complaints such as headache, pain in the teeth, burning lips and tongue, and muscle aches and pains together under the term "restlessness," for this would be the modality of expression for comparable symptoms in children. The observed minor differences probably reflect only age variations in patients' abilities to localize or describe sensations. It is interesting to note that hypertension occurred more frequently in adults, while tachycardia was more common in children. Fever, convulsions, coma, and transient lowering of the number of granulocytes in the peripheral blood have not been reported in adults. Since reactions considered severe or alarming oc-

curred in only 3 patients who received doses far in excess of recommended amounts, it appears that within the range of dosage considered useful children tolerate BAL as well as adults. Aside from occasional transient increases in temperature and pulse rate, evidence for a difference in tolerance is lacking.

As with adults,[14,15] reactions usually appeared 10 to 15 minutes following injection, and subsided spontaneously after 60 to 90 minutes. In like manner, reactions could be related not only to the size of the individual doses, but also to the cumulative amount of BAL given. Except with excessive initial amounts, they were delayed until after the second or third injection. No difference could be made out in the types and severity of reactions related to the age of patients studied.

TABLE III

REACTIONS IN ADULTS* AND CHILDREN WITH DOSES APPROXIMATING 5 MG./KG. BODY WEIGHT

Reactions	Ratio, adults:children
Nausea and vomiting	1.0:1.4
Restlessness	1.0:1.0
Vomiting	1.0:1.0
Pain at injection site	3.3:1.0
Salivation	4.4:1.0
Hypertension	2.2:1.0
Tachycardia	1.0:1.8
Reducing substances in the urine	1.0:1.0

* Sulzberger, Baer, and Kanof[14]
Modell, Gold, and Cattell[15]

Of reactions not previously observed in humans, the most notable were those resembling episodes of hypertensive encephalopathy—vasomotor changes, hypertension, convulsions, coma, and stupor—which appeared after excessive doses. With an initial dose of 40.5 mg. of BAL/kg., convulsions appeared in 45 minutes; with a dose of 25.0 mg./kg. repeated four hours later, they appeared 90 minutes after the second injection. A reaction more frequent and apparently peculiar to children was fever following the second or third injection; this persisted until BAL was stopped. It occurred in 8 of 27 patients who had more than 3.0 mg./kg. There was no other discernible cause for fever. The elevation in temperature never exceeded 1.6° C. except for two of the children who received huge doses.

After a transient lowering of the percentage of polymorphonuclear cells in the peripheral blood had been noted in several instances, we completed frequent and careful examinations for this phenomenon in 14 children in whom the dose of BAL ranged from 2.5 to 40.5 mg./kg. Among six patients given less than 4.5 mg./kg. we found it only once, but it occurred five times in a group of eight who had more than this amount. Altogether, 6 of 14 children exhibited this change; this sample is not large enough to permit valid comparisons related to individual and cumulative dosage or to age of patients. Except for excessive numbers of smudge cells seen after massive doses, there were no accompanying morphologic changes noted in blood smears, and there were no appreciable alterations in hemoglobin level, volume of packed cells, or total red and white cell counts. No studies of marrow were made, but the changes suggest a leuko-

toxic action primarily affecting the adult polymorphonuclear cells rather than the blood forming centers.

When BAL is given to normal adults, reactions follow more frequently than when it is given to individuals who have been poisoned.[14] We found this to be true for children who were treated "on suspicion." This might be expected to occur on a quantitative basis related to the number of BAL molecules not "bound" to arsenic. One might thus calculate the exact amount of BAL to be given, molecular weight for molecular weight, if the exact amount and type of ingested arsenic could be determined.

The plan we employ and recommend at present for the treatment of children for suspected or known arsenic ingestion is as follows:

(1) The stomach is lavaged with tap water as soon as possible.

(2) BAL (10%) with benzyl benzoate (20%) in peanut oil* is given at once in appropriate dosage (Table IV). Injections are made deep intramuscularly at rotating sites.

There is no method for precisely determining the dosage of BAL except when the exact amount of ingested arsenic is known. In principle, a particular quantity of BAL

TABLE IV

BAL FOR ARSENICAL POISONING*

	Individual dose mg./kg.	Number of injections	Intervals, hours
On suspicion	2.5	3–6	4–8
Mild symptoms	2.5–3.5	6–12	4–8
Severe symptoms	3.5–5.0	6–12	4–8

* Together with general and supportive measures as indicated.

is required to neutralize any given amount of arsenic. This should be given as rapidly as possible without using an individual dose large enough to produce BAL reactions. If reactions of BAL intoxication do occur, then it seems fair to assume that the amount of arsenic actually ingested was smaller than originally surmised. In this case, of course, one would naturally give the smaller number of injections suggested in Table IV. To minimize the occurrence of side reactions and cumulative effects the individual dose should not exceed 5.0 mg./kg. and the interval between injections should be no shorter than 4 hours. Larger doses can and have been used, but situations requiring them will probably arise very rarely. When the patient has been placed (from history and symptoms) into one of the groups shown in Table IV, individual doses may be chosen therefrom and utilized at frequencies and intervals fulfilling these criteria.

If treatment is undertaken because of suspicion of arsenic ingestion a small dose may be given for a short period—i.e., 2.5 mg./kg. every four hours for six doses. When it is apparent from the history and symptomatology that the amount of ingested arsenic exceeds 1.0 mg./kg. body weight—an intake potentially threatening life—larger individual doses (3.5-5.0 mg./kg.) may be employed for longer periods. Those using the drug for treating adults have set the precedent of "tapering-off" the number of daily doses according to such a scheme as the following:

* Obtainable in ampoules from Hynson, Westcott, and Dunning, Inc., Philadelphia, Pa.

Day of Treatment	Interval (Hours)	Number daily Injections
1	4	6
2	6	4
3	8	3
4	12	2
5–7	24	1

No "routine" can be established. The decision to continue into the second day with larger doses at frequent intervals, to taper-off rapidly or to discontinue the drug is best arrived at by assessment of the clinical status of the patient after 24 hours of therapy. Levels of urinary arsenic excretion, if facilities for their measurement are available, can be used to determine when the drug may be discontinued. Lacking this means, the alleviation of the symptoms of poisoning are a sufficiently accurate guide.

(3) Usual methods are employed for the correction of fluid and electrolyte deficits and medical shock.

(4) We have observed no cutaneous reactions, wheezing or other such allergic phenomenon.[14,16] The reactions we described earlier are ordinarily clearcut, and have made their appearance within ten to ninety minutes after any injections, usually the second or third. With recommended doses, none of these have seemed serious; evidences suggesting hypertensive encephalopathy call for reevaluation or recalculation. With BAL, as with diphtheria antitoxin, correct indications certainly justify occasional minor side effects.

Summary

BAL is an effective chemical antidote for arsenic poisoning. We have reported our observations after its use in treating 42 children who ingested this poison. During this experience, we have noted a number of side effects; with proper doses, none of these seemed serious. Recommendations have been made concerning applications of this drug, which should prove useful in one of the common pediatric emergencies.

Acknowledgments

We wish to express our appreciation to Miss Norma Lee Swazy of the Charity Hospital Laboratories for her help in the hematologic studies.

References

1. Report of the Council on Pharmacy and Chemistry, American Medical Association, 'BAL' (British anti-lewisite) in treatment of arsenic and mercury poisoning, J.A.M.A. 131:824, 1946.
2. Peters, R. A., Stocken, L. A., and Thompson, R. H. S., British anti-lewisite (BAL), Nature 156:616, 1945.
3. Ryder, H. W., Cholak, J., and Kehoe, R. A., Influence of BAL on human lead metabolism, Science 106:63, 1947.
4. Gilman, A., Allen, R. P., Philips, F. S., and St. John, E., Clinical uses of 2,3-dimercaptopropanol (BAL); treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbitol and BAL glucoside, J. Clin. Investigation 25:549, 1946.
5. Longcope, W. T., Luetscher, J. A., Jr., Clinical uses of 2,3-dimercaptopropanol (BAL); treatment of acute mercury poisoning by BAL, J. Clin. Investigation 25:557, 1946.
6. Davison, R., BAL therapy of dermatitis caused by injections of gold salts, Stanford M. Bull. 5:37, 1947.
7. Braun, H. A., Lusky, L. M., and Calvery, H. O., Efficacy of 2,3-dimercaptopropanol (BAL) in therapy of poisoning by compounds of antimony, bismuth, chromium, mercury and nickel, J. Pharmacol. & Exper. Therap. (supp.) 87:103, 1946.

8. Telfer, J. G., Use of BAL in lead poisoning, J.A.M.A. **135**:835, 1947.
9. Waters, L. L., and Stock, C., BAL (British anti-lewisite), Science **102**:601, 1945.
10. BAL in oil for treatment of severe mapharsen reactions, Bull. U. S. Army M. Dept. **4**:327, 1945.
11. Eagle, H., and Magnuson, H. J., Systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL), Am. J. Syph., Gonor. & Ven. Dis. **30**:420, 1946.
12. Eagle, H., Magnuson, H. J., and Fleishman, R., Clinical uses of 2,3-dimercaptopropanol (BAL); systemic treatment of experimental arsenic poisoning (mapharsen, lewisite, phenyl arsenoxide) with BAL, J. Clin. Investigation **25**:451, 1946.
13. Wexler, J., Eagle, H., Tatum, H. J., Magnuson, H. J., and Watson, E. B., Clinical uses of 2,3-dimercaptopropanol (BAL); effect of BAL on excretion of arsenic in normal subjects and after minimal exposure to arsenical smoke, J. Clin. Investigation **25**:467, 1946.
14. Sulzberger, M. B., Baer, R. L., and Kanof, A., Clinical uses of 2,3-dimercaptopropanol (BAL); studies on toxicity of BAL on percutaneous and parenteral administration, J. Clin. Investigation **25**:474, 1946.
15. Modell, W., Gold, H., and Cattell, M., Clinical uses of 2,3-dimercaptopropanol (BAL); pharmacologic observations on BAL by intramuscular injection in man, J. Clin. Investigation **25**:480, 1946.
16. Sulzberger, M. B., Baer, R. L., and Kanof, A., Clinical uses of 2,3-dimercaptopropanol (BAL); skin sensitization to BAL, J. Clin. Investigation **25**:488, 1946.
17. Carleton, A. B., Peters, R. A., Stocken, L. A., Thompson, R. H. S., Williams, D. I., Storey, I. D. E., Levvy, G. A., and Chance, A. C., Clinical uses of 2,3-dimercaptopropanol (BAL); treament of complications of arseno-therapy with BAL, J. Clin. Investigation **25**:497, 1946.
18. Longcope, W. T., Luetscher, J. A., Jr., Wintrobe, M. M., and Jäger, V., Clinical uses of 2,3-dimercaptopropanol (BAL); treatment of arsenical dermatitis with preparations of BAL, J. Clin. Investigation **25**:528, 1946.
19. Luetscher, J. A., Jr., Eagle, H., and Longcope, W. T., Clinical uses of 2,3-dimercaptopropanol (BAL); effect of BAL on excretion of arsenic in arsenical intoxication, J. Clin. Investigation **25**:534, 1946.
20. Hughes, W. F., Jr., Clinical uses of 2,3-dimercaptopropanol (BAL); treatment of lewisite burns of eye with BAL, J. Clin. Investigation **25**:541, 1946.
21. Sulzberger, M. B., and Baer, R. L., Development and use of BAL, J.A.M.A. **133**:293, 1947.
22. Goodman, L., and Gilman, A., The Pharmacologic Basis of Therapeutics, The Macmillan Co., New York, 1941, p. 740.

SPANISH ABSTRACT

El BAL en el Tratamiento de la Intoxicacion Arsenical

Experiencias realizadas con el uso del BAL (2,3-dimercapto-propanol) en 32 niños que habian ingerido arsenico han sido realizadas. Esto fue hecho para determinar la frecuencia, severidad y tipo de reacciones causadas por el BAL a fin de afirmar el criterio de seguridad para sugerir su empleo en determinadas dosis para el uso de los niños. El problema se enfoca por el estudio de la ingestion accidental de arsenico respaldada asi mismo por ensayos clinicos y experimentales en que el uso del BAL fue discutido.

Despues del contraste en los efectos del BAL en niños y en adultos fue posible arreglar sin embargo una tabla de dosificacion para su uso en el tratamiento de la ingestion arsenical de niños; comparando los resultados observados en estos cuarenta y dos casos con aquellos en los que se empleo los antiguos metodos siendo posible concluir que el BAL es en efecto un antidoto quimico de gran seguridad y muy efectivo para los niños que hayan ingerido arsenico.

Un plan del tratamiento empleado por el BAL es aqui presentado.

1430 Tulane Ave.

Pediatrics

VOLUME 1 MARCH 1948 NUMBER 3

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

REVIEW OF PRIVATE PRACTICE: PEDIATRICIANS AND GENERAL PRACTITIONERS

By JOHN P. HUBBARD, M.D. AND SAMUEL ZIBIT, M.P.H.
Washington, D.C.

THE preceding paper* has described a composite picture of the total volume of medical service for children in eight selected states. This summary has included medical care and health supervision given to children in hospitals, clinics, health conferences and by physicians in private practice. We may now examine in more detail one part of this total picture: private practice of pediatricians and general practitioners.

It should be kept clearly in mind that we are dealing only with physicians in private practice. Medical care rendered to children by those who are engaged in full-time academic positions is, for the most part, inseparable from hospital services; and, therefore, has not been included as a part of private practice. Excluded, also, are those physicians in administrative and research activities and those employed by federal, state and local health agencies.

For the purposes of this Study we have defined a pediatrician as a physician who says that he limits his practice to children. According to this definition, the Study listed 3,487 pediatricians in private practice in the United States; nearly one-half of these are members of the Academy, Table I. As of January 1947 the membership of the Academy within the United States was 1,909. Eighty per cent of this membership was engaged in private practice. An item which may be of considerable interest to the American Board of Pediatrics is the fact that of all pediatricians practicing in the country 51% are certified.

The distribution of pediatricians, indicated on a map of the United States (Fig. 1), shows a heavy concentration in the northeastern part of the United States. New York,

From the American Academy of Pediatrics, Study of Child Health Services, John P. Hubbard, M.D., Director, with the cooperation of the U. S. Public Health Service and the U. S. Children's Bureau.

Read December 9, 1947 at the Annual Meeting of the American Academy of Pediatrics, Dallas, Tex.

* Sisson, W. R., Bain, Katherine, Britten, R. H., Pennell, Maryland Y., Hubbard, J. P., Total volume of medical care for children based on an analysis of eight states, Pediat. 1:227, 1948.

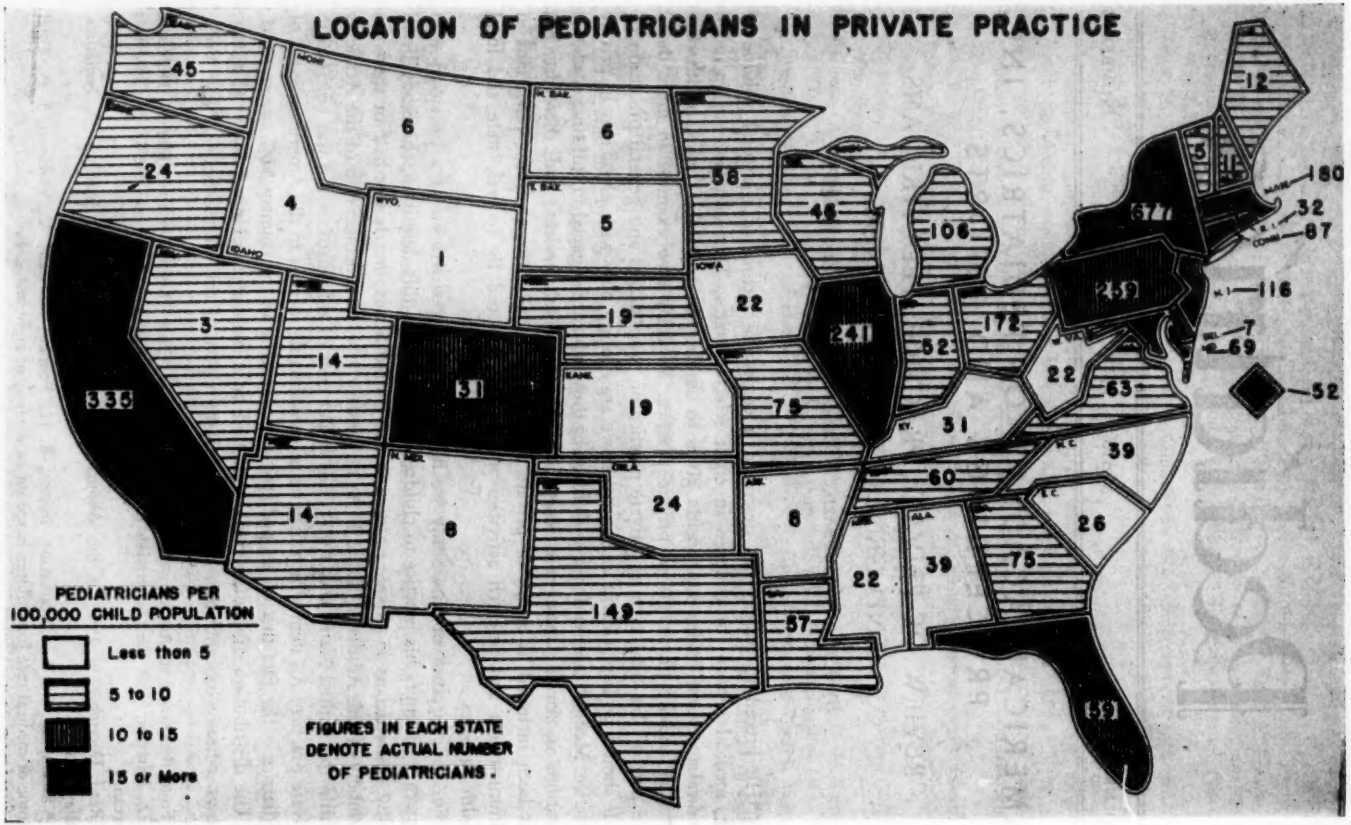
LOCATION OF PEDIATRICIANS IN PRIVATE PRACTICE
45
24
4
6
6
1
5
3
14
31
19
14
8
24
149
58
48
22
19
79
241
106
52
172
31
60
8
22
39
75
87
12
5
180
32
87
116
7
69
52
22
63
39
26
59
336
PEDIATRICIANS PER
100,000 CHILD POPULATION
Less than 5
5 to 10
10 to 15
15 or More
FIGURES IN EACH STATE
DENOTE ACTUAL NUMBER
OF PEDIATRICIANS.

FIG. 1

New Jersey and Pennsylvania combined account for 1,152, or approximately one-third of the pediatricians of the country. The concentration of pediatricians in urban centers is emphasized further by the fact that 75% of those in private practice are located in cities of 50,000 or more population. Approximately one-half are in or near the twelve major cities of the United States, in the group of counties which we have classified as greater metropolitan.

In the accompanying table, Table II, we have illustrated certain factors which appear to influence the distribution of pediatricians. For the eight states selected for this preliminary report, we have listed the number of pediatricians in relation to child popula-

TABLE I. PEDIATRICIANS IN THE UNITED STATES, 1946

	Number	*Per Cent*
Pediatricians in private practice	3,487	100
Academy members	1,535	44
Diplomates	1,780	51
Academy membership (U. S. A.)	1,909	100
In private practice	1,535	80

TABLE II. FACTORS RELATED TO LOCATION OF PEDIATRICIANS

State:	Pediatricians per 100,000 children	Income per capita 1943-45	Hospital Beds per 1,000 children	Children as per cent of total population
Maryland-District of Columbia	19	$1,250	19	23
Illinois	13	1,300	16	24
New Hampshire	9	900	18	26
Oregon	7	1,275	15	27
Montana	4	1,125	21	32
New Mexico	4	750	9	40
Alabama	4	650	6	36
North Carolina	3	675	8	36

tion, per capita income, and the number of beds in general hospitals. It is evident that a pediatrician prefers to practice in areas of relatively high per capita income, where at the same time he is more apt to have sufficient beds to care for his patients than in less wealthy areas. Fewer pediatricians are found in the areas less favored with dollars and hospital beds, although it is these same areas where children form a larger proportion of the population.

The influence of medical schools on the location of practicing pediatricians is very striking. There are obvious advantages in proximity to a major teaching center with its consultant and laboratory services and the stimulation to be gained from contact with hospital staffs and students. Of the pediatricians in private practice, one-half are in cities with medical schools.

What proportion of child care is given by general practitioners, by pediatricians and by other specialists? Figure 2 shows that in the eight selected states 75% of the child care given by physicians in private practice is given by general practitioners, in comparison with 12% given by pediatricians and 13% by other specialists. In states where the number of pediatricians is relatively few, children are, of course, cared for to a greater degree by general practitioners, as for example in New Mexico where 84% of the visits to children are made by general practitioners in comparison with 9% made

by pediatricians. On the other hand, in an urban area such as the District of Columbia where there is a higher proportion of pediatricians, 45% of the visits to children are rendered by general practitioners in comparison with 24% of the visits made by pediatricians.

How many children are seen on an average day or in an average week by an individual pediatrician or general practitioner? Tabulation of the data shows that a pediatrician sees, on an average, 16 patients a day. Since this is an average for every day of the week, including Sunday, it follows that he sees about 112 patients a week or nearly 500 patients

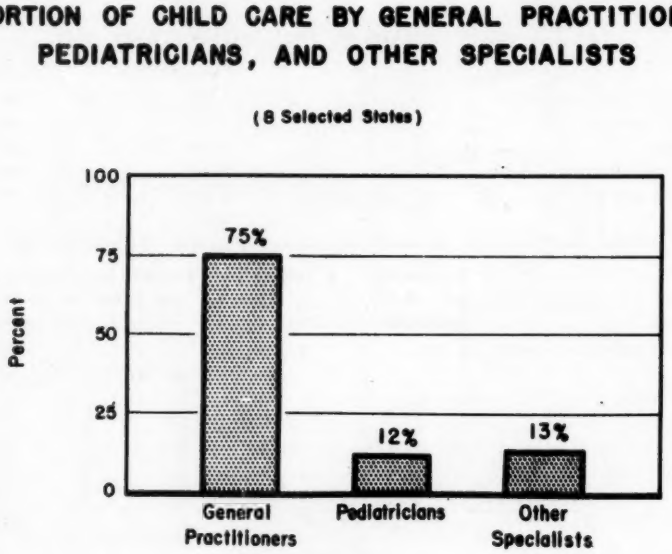

FIG. 2

a month. The individual general practitioner sees about a third as many children as the individual pediatrician (about 5 a day or 150 a month), but at the same time there are about 20 times as many general practitioners as there are pediatricians, so that three-quarters of all visits for children are made by general practitioners.

Drawing conclusions from the number of visits made to children is dangerous. It is probably true that more visits mean better care, but this must be accepted with reservations. A pediatrician who sees 85 patients a day, spending only a few minutes with each, increases the score in his community for the total volume of medical care, but it must be admitted that he does not serve an individual patient as well as the physician who sees fewer patients a day, giving more time to each. We have questioned reports of such large numbers of patients seen daily by individual physicians. Although the average is 16 patients a day per pediatrician, we now know that 85 patients a day seen by a single pediatrician is not an exaggeration. It not only can happen but does happen, with the aid of a battery of examining rooms and nurses to undress and weigh the patients and hand out diet slips.

It is very clear, as already mentioned in describing the total volume of medical care, that much of the information we have gathered points to deficiencies in isolated rural

areas. However, when comparisons are made between urban and rural areas, it is important that we should keep in mind certain limitations of this Study. We have obtained no information on health services received by "dead end kids" or white collar families in our large cities in comparison with the wealthier child in the same city. This Study has been designed to show variations in health services from a geographic point of view. No attempt has been made to compare health services in relation to economic social

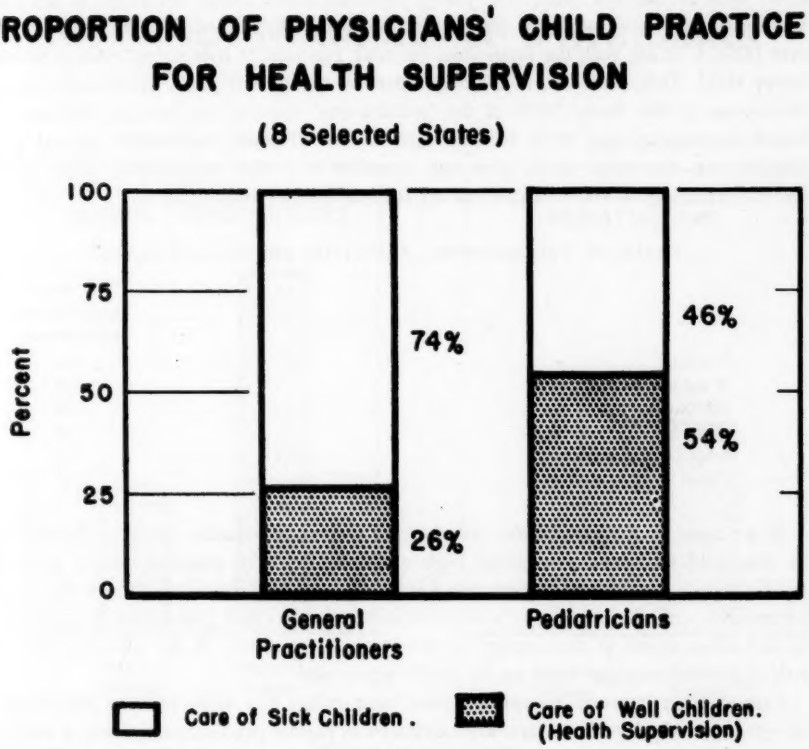

FIG. 3

levels of individual communities or cities. Despite the services of the free clinics and health centers in cities, a city child of an indigent family may be just as isolated from good medical care as the child in an isolated rural county.

One of the aspects of private practice which we have been most anxious to determine is the proportion of the average day's work given to health supervision of well children in comparison to medical care of sick children. Not so many years ago, the pediatrician's time was taken up in the care of children afflicted with diseases that have now largely disappeared; such as, diphtheria, dysentery, and the cholera infantum of summer months —to mention only a few. As these diseases have diminished in morbidity and severity, the pediatrician, and general practitioner, too, have given more time to the protection of health and less to the care of the sick. Are physicians being taught in medical schools and hospitals to give the type of care that will be demanded by their patients?

In medical schools and teaching hospitals, the student, interne and resident are taught

the diagnosis and treatment of disease; the rarer and more obscure the case, the more interest it arouses. Well-baby clinics are less exciting and they take relatively less of the time of interne or resident. Then one day the young physician emerges from the protection of a hospital and opens an office. A mother brings a young infant to see him, his first private patient, her first baby. She wants to know how many hours her baby should sleep, how much she should play with him or leave him alone. In short, she wants to know how to rear her child. The young physician could advise her better if her baby had erythroblastosis fetalis, for his training has been chiefly concerned with disease and very little, if at all, with the intangible, yet vital, function of helping to create a healthy, happy child. This, however, is the major part of the pediatrician's daily work. During the course of this Study, 54% of the pediatricians' visits on an average day were for health supervision and 46% for the care of sick children. Individual general practitioners, on the other hand, give less attention to health supervision; 26% of the general practitioners' visits for children are for health supervision (Fig. 3).

TABLE III. PROFESSIONAL ACTIVITIES OF PEDIATRICIANS

	Per cent of pediatricians participating
Teaching	37
Ward rounds	58
Out-patient clinics	44
Child health conferences	28
School health services	14
Other health activities	18

If we agree to the assumption that there is a direct relationship between the per cent of well-child visits and a relatively high quality of pediatric practice, honors go to the Pacific states, for in that region two-thirds of the pediatricians' visits are for health supervision, and the number of well visits in relation to child population is higher than in any other region of the country. In the southeastern states, on the contrary, less than half of the pediatricians' visits are for health supervision.

Certain other items of information have been included in order to learn something of the extent to which pediatricians who, although in private practice, participate in activities outside of private practice, such as teaching, ward rounds and what might be called pediatric public health. On the records for a 28-day period, a question was included asking whether or not during this period any time was spent in child health conferences, school health services, out-patient clinics, hospital ward rounds, teaching, and other general health activities. It is gratifying to see (Table 3) that about one-third of those who reported on this item found time during their busy practices to do some teaching. About one-half gave some time to hospital ward rounds or clinics, and a considerable number participated in pediatric public health activities.

Considerable interest has been focused recently on the upper age limit of pediatric practice. To an increasing degree pediatricians are considering the problems of adolescence to be within their proper field, in addition to which it is only necessary to remind you that the contentious Pepper Bill of 1945 defined a child as any person below the age of 21. What do pediatricians report as the upper age limit of their patients? Of the pediatricians recorded by the Study, 60% stated that they take care of patients beyond the 15th birthday. Actually, however, only 3% of pediatric practice is given for patients over 15 years

of age. About 13% reported that they took care of patients beyond 18 years of age. On the other end of the scale, it is somewhat surprising to learn that there are a few pediatricians, mostly in the northeastern and central states, who limit their practice to patients 10 years of age or younger.

At the outset an attempt was made to gain some information on the extent to which pediatricians are used as consultants by general practitioners and, on the other hand, the

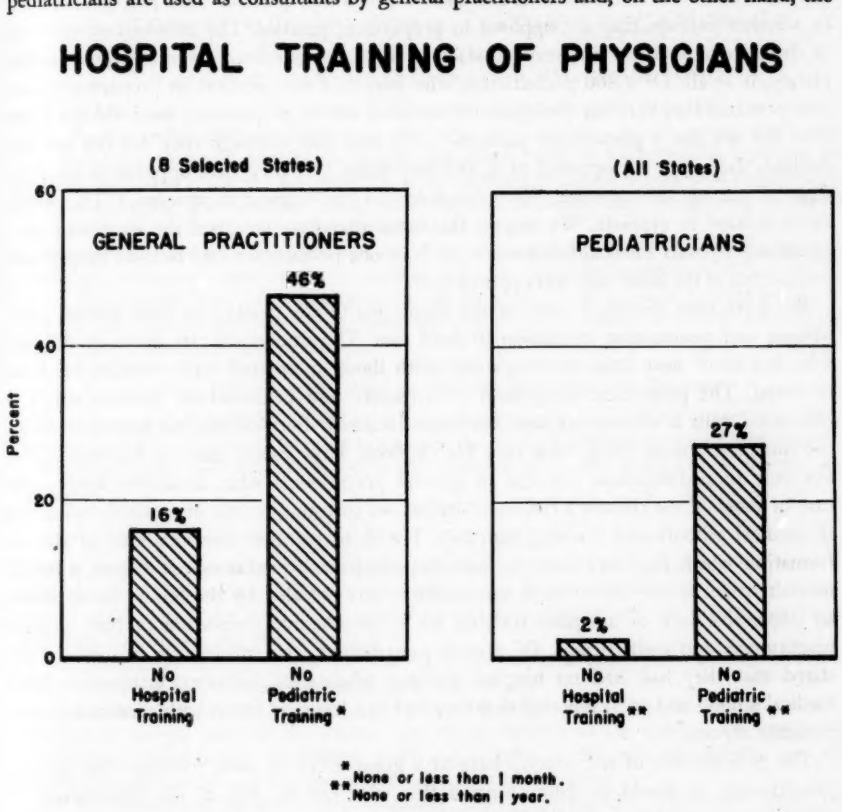

FIG. 4

extent to which pediatricians refer their patients to other specialists. It has been very difficult to obtain accurate information in this regard. We have, however, answers to three questions which may be considered indicative of the amount of general practice taken care of by the pediatrician. The three questions selected for this purpose were: Do you care for your patients for (a) fractures, (b) tonsillectomies, and (c) minor surgery? From these three spot questions, we hope to learn how far pediatricians cross over into what may be considered the field of the surgeon. The wording of this question was perhaps somewhat ambiguous since a physician might consider that he was taking care of his own patient for a tonsillectomy if he was in charge of the case, although he did not perform the actual surgery. However, it is fair to assume that for the most part this question was interpreted as we had intended; that is, if the answer was yes, it meant that the pediatrician did the tonsillectomy himself. Of the 2,833 pediatricians who

answered this question, 12% reported that they cared for their own patients for tonsillectomies, 16% for fractures, and 52% for minor surgery. Although minor surgery was not defined, the important aspect of this third item is that half of those reporting either did not do, or perhaps did not consider themselves qualified to do, minor surgery for their own patients.

Pediatricians were also asked the extent to which they practice on a prepayment basis or whether perhaps they are opposed to prepayment practice. The information obtained in these items is again not very satisfactory, since the questions were answered incompletely, if at all. Of 2,800 pediatricians who answered the question on prepayment practice, 600 said they care for their patients on some sort of prepayment basis. Of the 2,200 who did not use a prepayment method, 1,200 said that although they did not use this method, they were not opposed to it, and 900 stated that they were opposed to the principle of prepayment practice. (One hundred did not express an opinion.) This opposition is hard to evaluate. We suspect that some may have confused the issue with government proposals for health insurance. At least one pediatrician said he used prepayment practice but at the same time was opposed to it.

We have now described some of the highlights of the practice of both general practitioner and pediatrician in relation to child care. The amount of care given to children who live in or near cities in comparison with those in isolated rural counties has been reviewed. The proportion of general practitioners' and pediatricians' practice which is concerned with health supervision has been discussed. But nothing has been said about the qualifications of those who care for children. How much training has been given not only to pediatricians, but also to general practitioners who, as shown above, take care of most of the country's children? Before we turn to a review of pediatric education in medical schools and teaching hospitals, I wish to mention one final part of the information which has come directly from the physicians' questionnaires. Figure 4 brings into sharp focus one of the most outstanding facts revealed by the Study, for it shows an impressive lack of adequate training for a considerable proportion of both general practitioners and pediatricians. Of general practitioners who reported on this item, 16% stated that they had had no hospital training whatsoever following graduation from medical school, and 46% reported that they had had less than one month's internship on a pediatric service.

The pediatricians of the country have as a group received more training than general practitioners. It would be astonishing if this were not so. But of all pediatricians in private practice, 27% indicate that they have had either no pediatric internship or less than one year of internship on a pediatric service. Only about a half of the pediatricians in private practice have had more than two years of hospital training. Furthermore, our data show that this lack of adequate hospital training found among pediatricians can not be explained on the basis that these physicians are in the older age groups and had their hospital training before there were as many pediatric internships and residencies as there are today.

When we realize that some medical schools give the student very little opportunity to come directly in contact with child patients, this lack of hospital training after graduation from medical school becomes even more significant. The next paper, to be published in the April issue of PEDIATRICS, will describe in more detail the curriculum of pediatic departments along with other aspects of pediatric education in medical schools.

2346 Massachusetts Ave.

Special Report
From the Committee for the Improvement of Child Health

A Recommendation for FEDERAL SUPPORT FOR PEDIATRIC EDUCATION

The Health of the Nation Depends on the Health of the Child

The number one health problem of this country is not any one aspect of medical care. Cancer, heart disease, mental illness, important in themselves, are less vital to the nation's well-being than the general health of its children. Organic and mental health of adults depend largely on the care they received as children. Only in old age is the incidence of disease as high as in childhood; in no other age group does disabling disease strike as often. In infancy the very survival rate varies directly with the availability and quality of medical care.

The need for preventive, diagnostic, and curative services of high quality for *all children* has been established and agreed upon by the government, organized medicine, voluntary agencies and the public. Furthermore, there is general agreement on the need for *improvement* of child health. So much evidence has already been givn on the subject that the case for better medical care and health supervision for children is well established.

Better Child Health Depends on More Well-Trained Doctors

How is better medical care for children to be achieved? In the last analysis, success in this field depends not so much upon the physical facilities of the hospital, the laboratory or the pharmacy as upon the judgment and skill of the individual physician. This skill is a result of training and experience.

Deficiencies in Pediatric Training

As a step toward better and more evenly distributed health services for children, the American Academy of Pediatrics has conducted a nation-wide study of all factors involved in the medical care of children in the United States—hospitals, community health services, private practice of physicians and dentists, and pediatric education.

The preliminary findings of the Study reveal a startling lack of adequate training of a considerable portion of both general practitioners and pediatricians.

On an average day, about 450,000 children are seen by physicians in private practice. General practitioners provide 75% of the medical care of the children of the country. Yet nearly half (46%) have had practically no hospital training in pediatrics; 16% have reported that they had no hospital training whatsoever following graduation from medical school.

Of all pediatricians in active practice (about 3,500), approximately one-quarter report less than a year spent in hospital work in pediatrics following graduation from medical school. Among these are many in the younger age groups, which indicates that medical education is now failing to provide adequate training to many who are daily becoming responsible for the health of our children.

Unequal Distribution of Medical Care

The Study is also revealing in specific detail certain inequalities in the amount of medical care received by children in different parts of the country. In some areas children receive only half as much care as in other areas. This lack of adequate medical care arises from geographic and economic factors. Children in rural areas are handicapped particularly in specialist care, clinic care and the highly skilled diagnostic and treatment services—those very services which have been agreed upon as the right of every child: the essential preventive, diagnostic and curative medical services of high quality.

Approved by the Executive Board at special meeting in Chicago, February 8, 1948.

Need for Better Distribution of Well-Trained Physicians

These facts, now being sharply defined by the Academy's Study, point directly to the need for more physicians who are trained in the care of children, especially in the remote and rural areas. This need must be met before other health measures can be effected.

This need can be met only by strengthening pediatric education in medical schools and hospitals, for undergraduates and postgraduates, for general practitioners and pediatricians, and by bringing the benefit of this teaching to the child wherever he is.

Financial Support of Pediatric Education is Grossly Inadequate

Today any attempt to strengthen pediatric education is immediately blocked by the fact that medical schools are finding it increasingly difficult, if not impossible, to maintain even present standards.

Inadequate Budgets of Pediatric Departments

Personal visits to each of the 70 approved medical schools and their affiliated hospitals have brought into clear focus the precarious financial situation which limits pediatric education today. Departments of pediatrics, like other clinical departments, are operated frequently by voluntary staffs which serve entirely without recompense or with one so small as to represent merely a token. The average budget for the pediatric departments of the seventy medical schools is approximately $25,000 a year. Over a third of the pediatric departments work on teaching budgets of less than $10,000 a year; three of these have no regularly allocated funds for teaching.

It is recognized that the inadequacy of financial support of pediatric education is only one phase of a larger and more serious problem—the financial problem which confronts medical education in general. There are, however, certain factors which accentuate the difficulties of pediatric departments. Pediatrics is a branch of medicine—we prefer not to classify it as a specialty in the strict sense since it is really general practice for infants and children—which is historically younger than other specialties, as for example surgery. Therefore, departments of pediatrics in establishing their claim in respect to medical school budgets have had to compete, often unfavorably, with the more well-established departments. It is also a fact that the practicing pediatrician deals with families whose children are young and whose business incomes are just starting. In order to make a living, the pediatrician cannot rely on large fees from a few patients, but must carry a large and time-consuming load of patients. He is, therefore, limited in the amount of time he can give to teaching when no funds are available to reimburse him, as is usually the case.

The Cost of Special Training

The inadequate budgets of pediatric departments are only a part of the problem, although an important part. The cost of medical education to the student is such that unless he belongs to the privileged few, he has not the means to continue his course long enough to acquire special knowledge. The expenses of the medical student, including tuition, are about $2,000 a year for a period of four years. During his hospital internship, he usually receives little or no remuneration. By the time that a physician is undergoing his hospital training, he is in his mid- and often late twenties frequently married and with children. Little wonder that he tends to cut short his hospital work or that, if he has persevered through long specialist training, he then chooses to settle in an urban community where income from practice is relatively high and where he may make up his heavy expenses and late start.

Service Programs Need Doctors as Well as Dollars

The gross inadequacy of financial support for pediatric education stands in sharp contrast to funds available for medical services. An appropriation of $18,500,000 for one year has been made to the Children's Bureau for grants to states for maternal and child health services. This appropriation is approximately ten times the total annual budget of all medical schools for the purpose of training physicians in the medical care and health supervision of children. This wide difference should be considered in relation to the fact that all too often programs for maternal and child health are limited in scope and effectiveness by lack of well-trained physicians.

There is a fundamental misconception in pending bills for health legislation. The National Health Bill (S.545), and Health Insurance and Public Health Bill (S.1320), the School Health

Services Bill (H.R.1980 and S.1290), and the Maternal and Child Health Bill (S.1714) all propose, in one way or another, to meet existing needs in health services by providing Federal funds for the cost of medical care. Neither grants-in-aid to states for medical services nor compulsory health insurance will effect better or more evenly distributed medical care until well-trained physicians are available to render that care, especially in areas of need.

Federal Funds for Child Health Training

Federal support for child health training is required to provide more physicians, both general practitioners and specialists, better trained in the medical care and health supervision of children from birth through adolescence, as a means toward making available to *all* children of this country a more equitable distribution of health services of high quality.

Grants-in-aid to Medical Schools

The most urgent and immediate need is financial support of medical schools for teaching pediatrics. Money is needed, not so much for projects, as for salaries and the basic budgets of pediatric departments.

1. *To Increase Basic Teaching Budget of Pediatric Departments*

If these departments had an adequate budget, one that would provide salaries for full-time personnel and sufficient pay to part-time members of the staff to permit them to devote a reasonable proportion of their time to teaching without undue financial sacrifice, the teaching in these departments would be immeasurably improved.

2. *To Develop Decentralized Teaching and Rural Extension Services*

If these departments had an adequate budget, decentralized systems of pediatric teaching could be developed in order to bring better medical care to rural areas. Provision could be made for pediatric fellowships in the pediatric departments of an approved medical school. Such fellowships could not only enable recent graduates to continue special training, but could also make it possible to rotate them through periods of service in outlying community hospitals which had established affiliation with the teaching center. Provision could also be made for a senior member of the pediatric staff to conduct teaching ward rounds in such affiliated hospitals and to consult with local physicians. Thus, services of high quality could be extended outward from the medical schools. Hospitals being newly constructed under the Hospital Survey and Construction Act could be staffed with resident physicians. Better medical care could be brought into the very areas where deficiencies in medical care have been shown to exist.

3. *To Close the Gap Between Advancing Knowledge and Its Application*

This system of decentralizing medical care could also serve to keep physicians in outlying or rural areas abreast of the latest developments in the teaching centers, to produce better trained physicians and to close the gap between new knowledge in medical centers and its application to people in these rural areas. At the same time, better medical care would be brought to the very areas where medical services are now lacking. Furthermore, the community hospital and the health centers in outlying or isolated regions would be strengthened by being brought into close affiliation with university teaching centers. The training of the fellows themselves would be broadened by their experience and also they might be attracted to practice in the communities concerned.

Thus the process of strengthening pediatric education would appear in its proper light as a means of correcting the maldistribution of medical services and improving the medical care of the community.

Grants-in-aid to Hospitals and Other Teaching Services

Approximately 170 hospitals have been approved by the American Medical Association for pediatric residencies. These hospitals carry a considerable share of the responsibility for pediatric education, but they do not have adequate budgets for either teaching or service to their patients.

They are struggling for their very existence; unless immediate support becomes available, some will have to close their doors.

If these hospitals had increased funds available for teaching, better training could be given to interns and residents which would result in bringing better service to children under their care.

If these hospitals had increased funds, they too could provide pediatric fellowships and supplement medical school services described above.

Other agencies and institutions are concerned in pediatric education and the maintenance of high standards of teaching, as for example the certifying American Board of Pediatrics.

If such agencies, now limited in scope and function, had adequate financial support, they could strengthen pediatric education and be better able to serve medical schools, hospitals and the community.

Grants-in-aid to States for Pediatric Fellowships

Mention has been made of the gaps which the Academy's Study has revealed in child health services in rural areas and areas of economic stress. We knew before the Study was started that inequalities exist, but now we have exact information upon which to base positive action to fill the gaps within the states, within the counties, and within the cities. Physicians must be given inducements to attract them to these areas of need.

One half of the practicing pediatricians are located in cities having medical schools. States which do not have a medical school and which lack the opportunities which a medical school offers must take steps to make up for this handicap.

These needs could be met, at least in part, by grants-in-aid to states to provide for pediatric fellowships for medical school graduates committed to return to practice in an area of need within the state receiving the grant.

RECOMMENDATIONS

It is therefore proposed to provide for the improvement of child health by enabling medical schools, hospitals and other teaching services, and states to give more adequate training to physicians, both general practitioners and specialists, in regard to medical care and health supervision of children. For the purposes of meeting the need described above, it is recommended that an appropriation of $5,000,000 be authorized to provide for grants-in-aid to be made by the Federal Security Administration in direct support of pediatric education. Appropriations for subsequent years could be increased as may become necessary.

Grants-in-aid to Medical Schools

It is recommended that a sum of $2,500,000 be allocated for the first fiscal year to provide for grants-in-aid to approved medical schools to be used as directed by the head of the department of pediatrics. It should be clearly understood that these funds are to be considered as fluid funds to supplement the basic budget of the department for teaching purposes and that the allocation of such funds would not result in a decrease of funds allocated from other sources.

From the total allocation of $2,500,000, $20,000 should be earmarked for each of the accredited medical schools to be granted on request. The balance of funds from this allocation should be used to increase the basic amount of $20,000 for individual schools in accordance with need and student enrollment.

Grants-in-aid to Other Educational Institutions

It is recommended that a sum of $1,500,000 be allocated for the support of pediatric education not included in the above paragraph, such as grants for (1) scholarships or fellowships, (2) expenses for staff of pediatric departments when visiting affiliated or outlying hospitals for teaching ward rounds, (3) support for maintaining high standards of pediatric education, and (4) other purposes directly related to pediatric education.

Grants-in-aid to State for Pediatric Education

It is recommended that an amount of $1,000,000 be allocated to enable states to provide grants-in-aid for pediatric fellowships for graduates of approved medical schools. These fellowships

should be granted only with the understanding that recipients will be committed to return to practice in an area of need within the state receiving the grant.

These state fellowships should be not less than six months nor more than three years. Application for these fellowships should be made by the individual to the official health agency of the state which should approve applications only after receiving assurance that the fellow is acceptable to the hospital concerned.

Provision should also be made for the hospital to be paid from the state grant an amount sufficient to cover the expenses incident to the acceptance of such fellows.

Advisory Council on Pediatric Education

It is recommended that an Advisory Council on Pediatric Education should be created. This Council, which should consist of nine members, should include the chiefs of the Departments of Pediatrics of three approved schools of medicine; three members chosen from a panel of ten nominated by the American Academy of Pediatrics and three members who should be teachers or practitioners of medicine appointed at large. Appointment should be by the Federal Security Administrator; provision should be made for rotation and limitation of the term of service of individual members of the Council. The chairman of the Council should be elected by the membership of the Council. No grant could be made except as approved by the Council.

It is recommended that not more than 5% of the total appropriation of $5,000,000 should be allocated for the administration of this program, including expenses related to meetings of the Council and other conferences on pediatric education that may be called from time to time.

JAMES L. WILSON, M.D., *Chairman*
JOHN P. HUBBARD, M.D., *Director*
2346 Massachuetts Avenue, N.W.,
Washington 8, D.C.

Special Report
From the Committee on Reorganization

The Committee on Reorganization of the Academy has been appointed to study the constitution and by-laws of the American Academy of Pediatrics and make suggestions for such changes as may seem indicated. The Committee is anxious to call its existence to the attention of the members and request that they inform the Committee of any ideas that they may have relative to the organization of the Academy.

The State Chairmen discussed the problem at some length at the Annual Meeting in Dallas in December. It was felt that the Academy had grown to the point where its basic organization should be examined carefully within the near future.

It was specifically suggested that a formal organization be developed in the individual states so that the State Chairmen could be elected rather than appointed. It was also felt that the District and Alternate District Chairmen should be elected by the membership of the district concerned rather than by the membership of the entire Academy. Several State Chairmen expressed the view that members feel that they do not have a personal vote in the affairs of the Academy and that the organization of the Academy should allow for more active participation by individual members.

Respectfully,

Committee on Reorganization
JAMES MARVIN BATY, *Chairman*
FRANK H. LANCASTER
JOSEPH PALMA
EDWARD B. SHAW
FRANK VAN SCHOICK

WESTERN AREAL MEETING

Introduction

The first Areal Meeting of Districts VI, VII, and VIII was held in Salt Lake City on September 8, 9, and 10, 1947. There was an attendance of 350, the majority of whom were from District VIII, although there was a fair representation from other parts of the country. The time of year was ideal for a combined meeting and vacation.

The scientific sessions—which are presented here in abstract form—were held September 8 and 9, at the University of Utah Union Building, where there was also a good arrangement of the technical exhibits. Clinical sessions were held on September 10 at the Salt Lake County General Hospital. A very comprehensive and representative program was prepared by Dr. John A. Anderson, State Chairman of the Academy for Utah, and his committees.

Dr. Lee Forrest Hill, President of the Academy, reviewed the history of the Academy since its inception, its aims and policies as interpreted by the Executive Board and discussed the Child Health Study and some of its implications in planning for the future of child care.

The pediatricians of Utah and the local committees are to be congratulated for the excellent detailed planning of the scientific sessions, and clinics. The program of entertainment for all Academy members and their wives was a highlight of the meeting.

Vernon W. Spickard, M.D.
Chairman, District VIII

1. PATHOLOGIC CLASSIFICATION OF BULBAR POLIOMYELITIS,

by Joe R. Brown, M.D., Minneapolis, Minn.

The pathologic lesions of poliomyelitis consist of inflammatory cells in the perivascular spaces and infiltration of the parenchyma associated with acute and severe nerve cell injury. These changes may progress to focal areas of necrosis and to complete neuronal destruction respectively. The pathologic lesions involve chiefly the anterior horns but also implicate the meninges and occasionally the white matter. In bulbar poliomyelitis, lesions have been described in the cranial nerve nuclei, in other nuclear masses, and in the reticular substance.

Based on experience with 183 bulbar poliomyelitis cases in the 1946 epidemic it was possible to correlate clinical symptoms with the location of pathologic lesions and to divide bulbar poliomyelitis into five syndromes of importance in determining the treatment and prognosis. In addition, it was possible to indicate that anoxic damage super-imposed upon virus involvement often led to a fatal outcome.

1. In the Cranial Nerve Nuclei Group the bulbar lesions are limited to the nuclei of the cranial nerves. Involvement of the nucleus ambiguus produces paresis or paralysis of the pharynx and larynx leading to obstruction of the airway by the accumulation of saliva or by apposition of the vocal cords. The prognosis is good if an adequate airway is maintained.

2. In the Respiratory Center Group there are symptoms of irregularities in rate and rhythm of respiration with periods of apnea. Lesions are demonstrated in the ventral reticular substance at the level of the inferior olive. Prognosis is guarded, but one-third may recover if oxygenation is maintained.

3. The Circulatory Center Group of patients has very rapid pulse rate, elevated or low blood pressure, and low pulse pressure. Terminally there is a shock-like state. Prognosis is grave in this group and the lesions are located in the dorsal reticular substance of the medulla at the level of the inferior olive.

4. The Encephalitic Group has the general symptoms of anxiety, restlessness, tremors, convulsions, delirium and coma as well as focal neurologic findings. In some patients these symptoms may be due to actual inflammatory lesions in the hemispheres. In the majority of our patients these symptoms were attributed to anoxia and cleared up if adequate oxygenation was obtained.

5. Combined Bulbar and Cervico-thoracic involvement producing paralysis of diaphragm and intercostal paralysis, in addition to bulbar signs, comprised the fifth group. Lesions were present in the appropriate cord sekments in addition to the bulbar lesions described above. The problem of ventilation by use of a respirator required a guarded prognosis.

Pulmonary pathology was almost universal among the fatal bulbar cases. Acute pulmonary edema occurred as the result of forceful respirations against an obstructed airway. This was true especially when the mechanical respirator was used. Atelectasis followed the development of mucous plugs especially when humidification failed or paretic musculature prevented coughing. Extensive hemorrhagic pulmonary congestion of varied or uncertain etiology was very common. Pulmonary sepsis and pulmonary embolism were late complications.

2. ACTIVE AND PASSIVE IMMUNITY IN TETANUS, BY JOHN J. MILLER, JR., M.D., SAN FRANCISCO, CALIF.

A comparison of tetanus antitoxin production in children following active immunization with fluid, alum-precipitated, and aluminum hydroxide adsorbed tetanus toxoid is reported. Over a period of five years the latter was found to yield the highest titers. On the other hand, fluid toxoid was found to exert a more rapid secondary response and hence it is recommended as a wound booster.

The reports from the British and American Army Medical Corps on active immunization against tetanus during World War II are reviewed and applied to pediatric practice. The importance of maximal basic immunity, and repeated biennial reinjections of toxoid is stressed. In pediatric practice, at least, the goal should be maintenance of a high level of antitoxin at all times. Under these circumstances cases of tetanus from minor wounds can be expected to disappear. However, following compound fractures and gunshot wounds, rapidly developing, fatal tetanus may still occur occasionally despite active immunization. The incubation period in such massive intoxications may be too short for a wound booster to be of value. Resort to prophylactic tetanus antitoxin in such injuries is not contraindicated and may be life saving.

3. RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF PERTUSSIS, BY WILLIAM L. BRADFORD, M.D., ROCHESTER, N.Y.

During the past three decades pertussis, like certain other infectious diseases, has been characterized in the United States by a declining mortality rate, particularly in urban areas. However, in spite of this the case fatality rate under one year of age among hospitalized cases receiving the best available care remains between 3% and 10%. In New York State pertussis accounts for about 6% of the infant mortality rate.

A general renewal of interest in various aspects of the problem during the past fifteen years has led to the development of certain new diagnostic and therapeutic agents. The nasal culture method is a distinct improvement over the cough-plate method for the bacteriologic diagnosis of the disease. The use of agglutinogen as an intradermal test of immunity, although in need of further clinical confirmation, appears to be a useful method for the assessment of immunity. Better methods of diagnosis are necessary for there seems to be increasing number of mild cases.

The development of immune serum, both human and rabbit, and the apparent effectiveness of sulfadiazine and streptomycin are distinct contributions to therapy. However, these agents should supplement, rather than replace, good supportive care including the use of oxygen and special nursing in the management of therapy in the severely ill patient.

4. POLIOMYELITIS: A REVIEW OF THE NATURAL HISTORY, BY ROBERT WARD, M.D., NEW YORK, N.Y.

(Published as a Special Review, PEDIATRICS 1:132, 1948.)

5. PRIMARY RESPIRATORY DISEASES (PATHOGENESIS AND PREVENTION), BY JOHN M. ADAMS, M.D., MINNEAPOLIS, MINN

The common primary respiratory diseases in childhood include: the common colds, two known types: exudative tonsillitis or pharyngitis, influenza A and B; measles; scarlet fever, with and without a rash; and pertussis. There is an additional group of respiratory tract infections which

cannot be delineated definitely. These probably can best be classified as undifferentiated respiratory diseases. Most of these diseases may be mild, latent or severe by themselves or may be combined with secondary bacterial infection.

Two distinct types of mild respiratory disease have recently been described by the Respiratory Commission. These diseases have been transmitted to humans by filtrates free of bacteria. The first illness is characterized by cough, coryza, nasal obstruction and sneezing and has a one to two day incubation period. The second illness is characterized by sore throat and few nasal symptoms and has a five to six day incubation period.

Exudative tonsillitis or pharyngitis is one of the commonest diseases of childhood. The Respiratory Commission demonstrated that over half of these patients have neither bacteriologic nor serologic evidence of streptococcus infection. The disease may be very severe in infants over six months of age, but usually runs a self-limited course of three or four days. The patients in whom large numbers of hemolytic streptococci are found may be slightly sicker and tend to show more complications than in the non-streptococcus cases.

Influenza is an epidemic disease, the A form occurs at two to three year intervals, the B form at four to six year intervals. The onset of the infection is abrupt in infants and children, the temperature elevation is irregular or biphasic, and the patients appear actuely ill. Sore throat is a common subjective complaint and the pharynx appears beefy-red and inflamed in many of the patients studied by us in a proven epidemic due to Influenza A.

Most of the primary respiratory diseases are air-borne and invade the human host to produce a relatively mild disease. It is this disturbance in the host which may lead to development of so-called secondary bacterial disease. The carrier state is known to be common, and following a primary infection, organisms which are present in the upper respiratory passages increase in number and virulence. Acting synergistically, they may then be responsible for serious disease such as otitis media, mastoiditis, meningitis or pneumonia.

Prevention should be directed at the primary disease as well as the concerted infections. Isolation is an effective means; vaccines against Influenza A and B are effective. Gamma globulin will prevent measles passively, and there are good vaccines against pertussis. Control of the bacterial complications can be accomplished by means of the sulfonamide drugs or penicillin.

An additional preventive measure includes postural drainage. The abdominal or prone position permits better drainage of the respiratory tree and helps to prevent gravitation or aspiration of infected exudate into the lungs. Troublesome cough is often greatly relieved by postural drainage.

Specific polyvalent pneumococcus vaccines have been shown to be effective in the prevention of pneumoccoccic infections.

6. TRACHEOTOMY IN BULBAR POLIOMYELITIS,* BY ROBERT PRIEST, M.D., MINNEAPOLIS, MINN.

Experiences with tracheotomy during the Minneapolis epidemic of 1830 cases of poliomyelitis during 1946 are analyzed. Approximately 400 "bulbar" cases were reported. Seventy-five tracheotomies were done. Twenty-nine of these patients survived.

On the pediatric service at the University Hospital and at the Minneapolis General Hospital, tracheotomy was performed when the following indications existed: respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor; excitement and unmanageability causing the patient to resist pharyngeal aspiration; stupor of a degree sufficient to make the patient oblivious of accumulation of secretion in his airway; inability to cough effectively; pharyngeal pooling of mucous, vocal cord paralysis, or intralaryngeal hyperesthesia demonstrable by laryngoscopy.

On the adult neurologic service at the University Hospitals the criteria listed above were considered to be indications for tracheotomy. However, it was believed that tracheotomy gave the patient his best chance if done before cyanosis occurred, because cyanosis can be diagnosed clinically

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* Priest, R. E., Bores, L. R., Goltz, N. F., Tracheotomy in Bulbar Poliomyelitis, Annals Otol., Rhinol., and Laryngol. 56:250, 1947.

only when it is far advanced and when irreversible damage has been done to a central nervous system already damaged severely by the virus.

The detrimental effect of anoxia on the central nervous system is emphasized. We believe that this has been stressed sufficiently by only a few authors writing about bulbar poliomyelitis. We believe: (1) that tracheotomy improves the chance for survival of properly selected bulbar poliomyelitis patients, if done before anoxia has produced significant central nervous system damage; (2) that tracheotomy used in conjunction with various means for producing artificial respiration will enable some critically ill poliomyelitis patients to survive until natural recovery of damaged neural tissue can occur.

7. NITROGEN MUSTARD THERAPY OF LYMPHOMAS AND LEUKEMIAS, BY M. M. WINTROBE, M.D., AND CHARLES HUGULEY, M.D., SALT LAKE CITY, UTAH

(Abstract not Available for Publication)

8. ACIDOSIS IN YOUNG INFANTS, BY HARRY H. GORDON, M.D., DENVER, COLO.

The results of observations of the effect of ingestion of ammonium chloride on the acid-base excretion of three premature and three full term infants were presented. Two of the three premature infants showed a diminished ammonia and increased sodium excretion. One of these two infants and the third premature infant, the two smallest in the series, became listless and clinically dehydrated. This could not be correlated with the chemical findings in the urine or blood. Since the dehydrated infants gained weight during the observation, the possibility of shifts of water and electrolytes from extracellular to intracellular compartments was considered. It was suggested that the tendency of young infants to acidosis might be conditioned by disabilities in intracellular metabolism as well as by renal disability. The implications of the defects in homeostasis for therapy were discussed.

9. THE ROLE OF THE PEDIATRIST IN THE FIELD OF MENTAL HYGIENE, BY HENRY C. SCHUMACHER, M.D., CLEVELAND, OHIO

(Abstract not Available for Publication)

10. MODERN DRUG THERAPY OF EPILEPSY, BY LOUIS F. GOODMAN, M.D., SALT LAKE CITY, UTAH

(Abstract not Available for Publication)

11. MENTAL AND EMOTIONAL DISTURBANCE IN ADOLESCENTS, BY HENRY C. SCHUMACHER, M.D.

(Abstract not Available for Publication)

12. ENDOCRINE PROBLEMS IN THE ADOLESCENT, BY HARRY H. GORDON, M.D.

Certain general considerations influencing the diagnosis and treatment of endocrine problems in the adolescent were discussed. Growth and maturation in the somatic, genital, intellectual and emotional spheres may take place at different rates in the same individual and the complaints of parents and child may be derived from these differences. Some complaints and mistaken diagnoses of endocrine dysfunction stem from failure to recognize the wide limits of normality, or the effects of heredity and of environment, including diet, disease, and social factors, on symptoms.

The minor role of endocrine therapy in the treatment of complaints such as obesity, short and tall stature, and the major role of an approach to the problems of the patient as a whole were discussed. Indications were presented for the use of gonadotropins in the treatment of cryptorchidism. The difficulties in the differentiation between true hypogonadism and "delayed puberty" in both the male and female and the limitations of endocrine therapy were discussed. The special problems of thyroid disorders and diabetes mellitus in adolescents were briefly mentioned.

13. METABOLISM OF ADOLESCENCE AND ITS RELATIONSHIP TO DISEASE, BY JOSEPH A. JOHNSTON, M.D., DETROIT, MICH.

(From Author's Paper, Nutritional Requirement of the Adolescent and Its Relationship to the Development of Disease, Am. J. Dis. Child. **74**:487, 1947)

14. SOME OBSERVATIONS ON THE SO-CALLED HAND-SCHÜLLER-CHRISTIAN SYNDROME, BY FRANCIS SCOTT SMYTH, M.D., SAN FRANCISCO, CALIF.

The terminology Schüller-Christian disease has been adopted from the names of physicians who early described a syndrome of membranous bone involvement, diabetes insipidus, and exophthalmus. Too often the contributions of Hand are overlooked. Hand first ascribed the etiology to tuberculosis but later suggested a "neoplastic, benign, and myxomatous" nature. The suggestion of pituitary involvement where diabetes insipidus was present, together with the current interest in the pituitary at the time of Christian's report, led to an unwarranted emphasis on this endocrine as a factor.

Biopsy studies by Warthin subsequently fixed the attention on accumulation of foam cells in the affected area. It is thus often classified as a storage disease phenomena in which the cholesterol deposition suggests an abnormality of fat metabolism. However, a study of the blood transport of fat, the effect of diet, thyroid, lopocaic, choline and other factors, has failed to show any primary cholesterol metabolic defect.

In addition, experience with a small number of patients presenting this syndrome suggests that neither the triad (of membraneous bone, exophthalmus, diabetes insipidus) nor the foam cell on section are entirely reliable diagnostic aids. Involvement is by no means limited to the membranous bones; orbital plate involvement accounts for the occurrence of exophthalmus, and involvement of sella or contiguous areas for such instances as show diabetes insipidus. Autopsy shows the lesions generalized in the recticulum and of varied stages of granuloma development—small fresh collections of reticular cells passing into a mid-stage when the cells accumulate cholesterol as a "foam cell" no different in appearance from the ordinary fat-all and finally to a stage of sclerosis and hemorrhage. In our experience also the diagnosis has often been confused with chloroma, Ewing's tumor, osteitis fibrosa cystica, osteomyelitis—especially mastoiditis, etc. We suggest the disease is more common than is generally presumed. The recent suggestion of Wallgren, Farber, and Mallory, that Letterer-Siwe's disease—occurring in younger patients of about two years of age and associated with spleno-hepatomegalia with a malignant, rapidly fatal course—Schüller-Christian disease in older children with a better prognosis and eosinophilic granuloma of adults which by comparison is benign are manifestations of the same general process would seem logical. However, it must be admitted that, as with the foam cell, eosinophilia is not always present in the biopsy. One may also find instances of mitotic figures, although this is not usually mentioned.

While neither agglutination studies nor cultural studies support the view, Farber and others are again suggesting an infectious, possibly virus, etiology. Of equal merit is the consideration of a neoplastic condition (Hand). Our best results would seem to be associated with a combination of surgical excision and X-ray. While mitotic figures are not seen frequently in section, there remains the suggestion that, like the so-called "benign metastasising thyroid malignancy," a "mother" lesion may be involved. However, despite widespread bone involvement, we have not found phosphatase studies valuable nor radioactive phosphorus (in two cases) helpful. X-ray, as Sossman first described, remains the most valuable aid, but some patients would seem to run a mild course in any treatment and in one instance, it would seem likely that the extensive use of X-ray had aggravated an aplastic condition of the blood.

We have not included in this study the instances of xanthoma tuberosa nor that of secondary diabetes mellitus. It is our feeling that in the hyperchloseteremic types the condition is more likely one of cholesterol metabolism. There remains, however, the mystery in both types regarding the avidity for fat in the reticulum cells of these patients. Why do we not see extensive phagocytosis of fat in all hypothyroid patients with hypercholesteremia and in the nephrotic state accompanied by high blood cholesterol? It is apparent that our technics must develop to study the cell directly rather than to rely on the indirect evidence accumulated from chemical analysis of the transport—the blood.

15. THE VALUE OF RADIUM THERAPY OF LYMPHOID STRUCTURES OF THE NASOPHARYNX, BY DAVID A. DOLOWITZ, M.D., L. PAUL RASMUSSEN, M.D., E. B. HOLLEY, M.D., AND HAL WAKEFIELD, M.D., SALT LAKE CITY, UTAH.

A low grade chronic infection of the posterior pharyngeal lymphoid structures results in symptoms related to the lower respiratory and gastro-intestinal system. These symptoms appear to be related to the excessive production of mucus and mucopurulent material which arises from this area. The continuous or intermittent drainage of infected mucoid material from the partially obstructed recesses of the nasopharynx into the esophagus and stomach and into the trachea and lower respiratory tract produce many symptoms. The most commonly encountered were: chronic hacking cough, coryza, mouth breathing, snoring, nasal voice, anorexia, and restless sleeping. Less common but frequently encountered symptoms were: earache and hearing loss, low grade fever, gagging, vomiting, and choking. The gagging and vomiting were seen at mealtime. Several of the children examined showed evidence of swallowing large amounts of the mucopurulent material over a rather long period of time. The chronic presence of this mucus in the stomach appeared to produce poor appetite, nausea, and vomiting and contributed to a picture of nutritional inadequacy as measured by the Wetzelgrid technic. It was thought that the presence of excess mucopurulent material in the stomach contributed more to the picture of malnutrition than did the small degree of chronic infection present in the lymphoid structures of the nasopharyngeal region.

The use of nasal antibiotics, vasoconstrictors and long periods of sulfonamide therapy had failed to give lasting improvement. Radium therapy of nasopharyngeal lymphoid structures in 174 cases produced striking improvement in many of the symptoms listed above. The percentage of marked improvement for the following symptoms is given: cough, 89%; coryza, 92%; mouth breathing, 93%; improved appetite, 40%; and snoring, 94%.

16. STREPTOMYCIN IN CLINICAL PEDIATRICS, BY WILLIAM L. BRADFORD, M.D.

The discovery of streptomycin in 1944 by Waksman has already been given wide clinical application. Only five productive strains of streptomyces griseus have so far been identified. One of the original strains (18-16) came from a manured soil; the other (D-1) was isolated from the throat of a chicken.

When possible it is advisable to test the sensitivity of the organism in question before therapy is begun. However, clinical results have not always corresponded to those predicted by such a test. Adequate blood levels result within two hours after intra-muscular injection of streptomycin. A level of μg./cc. of blood is sustained after the parenteral injection of 0.6 gm./day. After intramuscular injection streptomycin appears in most of the body fluids and from 50% to 75% of a given amount is excreted in the urine within 24 hours. About one-fifth of the serum level value may be observed in the spinal fluid after intramuscular injection in cases of meningitis. This amount may or may not be inhibitory. Unlike penicillin, streptomycin, when inhaled into the respiratory tract, does not appear in the blood in significant amounts.

Various types of toxic reactions may result from the administration of streptomycin; such as local, histamine-like, sensitization and neurologic reactions. One of the most serious is deafness which probably results from degeneration and necrosis of the neurons in the eighth nerve nuclei.

Streptomycin is the best treatment for tularemia and is indicated in the treatment of certain gram-negative bacterial infections of the central nervous system, such as that caused by H. influenzæ. It is palliative in the treatment of tuberculosis, but constitutes a useful adjuvant to other accepted forms of therapy. It is effective in the treatment of bacteremia and of urinary tract infections when the organism is sensitive. In pertussis it brings about disappearance of the organism from the respiratory tract particularly when used as local treatment. In brucellosis and in salmonella infections it has not been highly effective.

One of the chief reasons for the failure of streptomycin as a therapeutic agent has been the readiness with which the organism may develop resistance. It seems probable that this results, according to Alexander and Leidy, from the emergence of sufficiently large numbers of resistant cells from the original bacterial population in a given infection.

17. THE TREATMENT OF INFANTILE DIARRHEA WITH STREPTOMYCIN AND AN ORAL AMIGEN MIXTURE, BY ELVIRA GOETTSCH, M.D., LOS ANGELES, CALIF.

In March 1945 a severe epidemic of diarrhea was observed. The morbidity was 40%; the uncorrected death rate was 20%; the corrected death rate was 7%. Bacteriologic studies in 18 critically ill infants revealed Esch. Coli in: (1) the ear cultures of four babies; (2) the catheterized urine of four other infants; and (3) in half the nasopharyngeal cultures taken. The treatment included the early use of oral amigen (a mixture of casein hydrolysate, glucose, and mineral salts), in addition to the customary replacement of parenteral fluids and sulfa-chemotherapy. The predominance of gram-negative organisms isolated from the nasopharynx, the ears, and the urine suggested invasion and its seemed that therapy with streptomycin might aid in similar cases.

Recently 20 infants under eight months of age with intractable diarrhea, who failed to respond to the usual parenteral fluid replacement, sulfadiazine and penicillin, were treated with streptomycin. In all infants the clinical response was dramatic, the temperature fell promptly and the stools improved in a short time. The course of four patients is presented in detail. One gram of streptomycin was given daily for 10 days; 62.5 mg. intramuscularly every three hours and 62.5 mg. orally every three hours.

18. PRIMARY "VIRUS" PNEUMONITIS IN INFANTS, BY JOHN M. ADAMS, M.D.

Primary virus pneumonitis of the newborn and of early infancy is characterized by an acute onset of sneezing, cough, dyspnea and cyanosis. Three distinct epidemics have been observed. The incidence of infection in each has been very high. However, not all of the babies develop pneumonitis, some having minor symptoms of sneezing and cought only. In the first two epidemics, 62% of the patients had the characteristic symptom of cough, dyspnea and cyanosis. The fever has been moderate to low, some infants showing none. There has been a definite correlation of mortality with the severity of symptoms and signs. The mortality rate in the first two epidemics was 20%. Prematurely born babies are very susceptible and their mortality rate is extremely high.

The diagnosis is made by the symptom pattern and by characteristic shadows seen in the X-ray film of the lungs. In addition, pharyngeal smears show epithelial cells in large numbers, and an almost complete lack of bacteria and polymorphonuclear leukocytes. The epithelial cells contain characteristic cytoplasmic inclusion bodies. The bodies may represent a change in the cytoplasm of the cell caused by a specific pneumotropic virus. When seen in large numbers they appear to have diagnostic significance. Their occasional presence in infants, older children, and adults unassociated with apparent disease or with only mild inflammatory reactions in the throat is not surprising as this agent appears to be ubiquitous in much the same way as the common cold. No adults coming in direct contact with the epidemic disease in infants have become ill with pneumonitis so far as we have been able to determine.

Pathologic studies of the lung sections reveal a highly characteristic picture. The prominent features are destruction and proliferation of bronchial epithelium, with peribronchial infiltration of mononuclear cells. Typical cytoplasmic inclusion bodies are found in the epithelial structures of the lung. These bodies have all of the characteristics of virus inclusions, and are morphologically identical to the bodies seen in the upper respiratory passages in the acute stage of the disease. They stain acidophilic with hematoxylin and eosin and also with Giesma stain. There appears to be a clear zone or halo about the inclusions. Their size varies in the lung section from 3 μ to 6 μ in diameter. In pharyngeal tissues greater variation in size is seen, and granules occur occasionally in the body of the inclusion. The pathologic picture is identical to that reported by most authors in atypical pneumonia, apart from the finding of cytoplasmic inclusion boides. An acute interstitial pneumonitis is the outstanding feature of the pathologic picture.

No beneficial results have been obtained from the use of sulfonamide drugs or penicillin except when secondary bacterial infection has been present. Oxygen, administered continuously, is of great benefit. More recently the use of pooled adult serum and concentrated human gamma globulin have been found to be helpful in moderating the disease picture. If given early, they probably have a prophylactic effect.

Attempts to transmit this disease to ordinary laboratory animals have failed, but we have been

able to produce a respiratory disease in newborn calves on the fourth day following intranasal inoculation. Typical cytoplasmic inclusion bodies were demonstrated in the nasal epithelium of the calves. By means of the Chamber's microdissection apparatus we have been able to dissect single inclusion bodies from epithelial cells for purposes of transmission.

19. PRACTICAL LABORATORY ASPECTS OF THE Rh PROBLEM, BY G. ALBIN MATSON, PH.D., SALT LAKE CITY, UTAH

To understand the laboratory aspects of the Rh problem it is necessary for the worker to possess a working knowledge of the heredity of Rh and the reciprocal nature of each variety of Rh with the corresponding Hr antigens. The relationship of the various agglutinogens, antisera, and genotypes of the Rh and Hr types were shown in a table.

Laboratory findings in three cases of hemolytic disease of the newborn were presented and briefly discussed. It was emphasized that with the aid of properly prepared anti-Rh and anti-Hr typing sera it is possible for the trained serologist to make a study of the hereditary blood factors in families having congenital hemolytic disease due to apparent Rh incompatability and thus, within limits, determine genotypes and the chances of having Rh negative and therefore normal babies or Rh positive and therefore erythroblastotic infants in such families.

The Rh antigen may stimulate in Rh negative individuals antibodies of more than one variety—agglutinating, demonstrable in saline diluent; blocking, demonstrable by using AB plasma or serum, or albumin as diluent of cells and serum; and a third order revealed by the more sensitive Coombs test. It appears that agglutinating antibody is the earliest variety to be formed in response to stimulation by Rh antigen and that blocking antibody appears somewhat later and is thought to be evidence of a greater degree of sensitization.

All Rh negative individuals who will need transfusions, especially over a long period of time, should receive only Rh negative blood. This is especially important in the case of girls and of women in the child bearing age who are Rh negative, since females thus sensitized with Rh positive blood may find their first-born Rh positive infant to be afflicted with hemolytic disease. Cases of women taken from our records who show a history of transfusion or of small intramuscular inoculations of Rh positive blood for morning sickness and whose first babies were afflicted or stillborn were presented.

Of the three Rh antigens the Rh_0 (D) is the strongest and most important since it is present in 85% of the white population. In testing a patient for Rh it is not absolutely necessary to test the erythrocytes with antisera of all three specificities. The obvious 2% error which will be made when using only the anti-Rh_0 (anti-D) typing serum is an error on the side of safety. In typing donors, however, it is important that the blood be tested with antisera of the three specificities since, for example, in an Rh negative patient sensitized against Rh′ (C) a reaction against the Rh′ (C) factor would surely occur if blood lacking the Rh_0 (D) antigen but containing the Rh′ (C) antigen were transfused into such a patient. A case of a severe transfusion reaction due to this sort of accident was presented.

In emergencies and in the absence of serums which may detect Rh′ (C) or Rh″ (E) antigens in Rh_0 negative (D negative) donors, the hospital laboratory may employ one of the newer more sensitive compatability tests which detect possible reactions due to Rh′ (C) or Rh″ (E) factors.

20. RHEUMATIC FEVER IN SCHOOL CHILDREN IN UTAH, BY WILLIAM RIGBY YOUNG, M.D., SALT LAKE CITY, UTAH

(Abstract not Available for Publication)

Round Table Discussion

RHEUMATIC INFECTION IN CHILDREN

ARILD E. HANSEN, M.D., *Chairman, Galveston, Tex.*, AND
GLADYS J. FASHENA, M.D., *Dallas, Tex.*

INTRODUCTION

Chairman Hansen: That we are here today bespeaks our interest in the problem of rheumatic fever. Undoubtedly some have come in hopes of finding new clues to a better understanding of a difficult problem, in spite of quite intimate knowledge of the field. Others may feel they have been pressed with variable agitations from many sources, hence desire to become more familiar with general features as well as details. From the viewpoint of the persons asked to conduct this Round Table Discussion, the same features apply; namely, the desire to gain exact information, yet help if possible in the clarification of points which are becoming generally accepted. The subject is broad, varied, indefinite and controversial at times even to the point of provoking emotional responses. Its importance is undisputed, the frequently cited comparatives and invectives in vogue may be mentioned as evidence:

"One of the chief causes of death in the school age child—responsible for more deaths in this age group in almost any year than the combined deaths from ordinary childhood diseases, e.g. diphtheria, poliomyelitis, scarlet fever, measles, mumps, with meningococcic meningitis thrown in—responsible for seven times the number of deaths as poliomyelitis in this age group—significantly more deaths than from all forms of tuberculosis—chief cause of death from heart disease in the young adult—and one of the chief causes of disability in children and youth—producing 'cripples who do not limp' also 'cripples who cannot even walk.' "

Textbook knowledge, perusal of current literature and personal consultation coupled with practical experiences allow one to comprehend the problem of rheumatic fever in childhood almost as well as the "expert". The question recently has arisen, "Who knows the problem of rheumatic fever?"—the pediatrician, the internist, the cardiologist, some other specialist or the general physician? The nature of the disorder itself has solved that question. The protean symptomatology, the capriciousness of diagnosis, the varied and bizarre course of the disease, the importance of nutrition, educational features and the psychologic and emotional phases may tax even the pediatrician though his field is broad indeed. As a corollary, it may be stated that if one really knows the subject of rheumatic fever, he is a pediatrician whether or not he realizes it. This has been brought to the fore in attempting to arrive at a decision as to: "Who should be the director of a rheumatic fever program?" As a matter of fact, it has been suggested that the theme for a Round Table Discussion should be community planning in relation to the problem. This is a highly important topic and certainly deserves free discussion, primarily because practicing physicians seeing children are in the first line of attack on the problems of which there is considerable public awareness and even social implications. The keynote is detection and prevention. They are the foundation stones in the practice of pediatrics. Partly because of rather meager experience with the communal phase of the subject but particularly because problems of diagnosis and management from the viewpoint of practicing physicians appear to deserve accentuation and definitely so, it has been decided to use the question and answer approach in conducting this Round Table Discussion. Most of the questions have been asked in various groups, although their arrangement will tend to follow more or less the classical (or prosaic) sequence. The idea to provoke questions from members of the round table discussions.

GENERAL FEATURES

Q. Has rheumatic fever actually increased in incidence? Is it simply the improved health of infants because of better feeding in addition to other preventive measures which accentuate its relative importance?

A. Undoubtedly, the importance of rheumatic fever is relatively greater. Contributing to this also may be the conquering of the problem of tuberculosis in infancy and childhood.

Q. The statement is often made that rheumatic fever is a disease of the poorer classes (poorly fed and poorly housed ? Hence, is it one which so much concerns the practicing pediatrician?

From the Annual Meeting, Dallas, Texas, December 8-11, 1947.

A. Would that this could be answered by the physicians whose own children have rheumatic fever.

Q. Do you have any idea why we as physicians have been rather slow to recognize the seriousness of the problem of rheumatic fever?

A. In part, it may be that the clear cut etiology has not been discovered; and, in part, the difficulty of correlating the often mild and rather obscure symptoms which result in serious heart damage later and even ultimately in death. These seem to be remotely related on superficial consideration in the majority of instances.

Q. Did not our pioneer physicians who so often were astute clinical observers mention the relationship between arthritis and heart damage?

A. Strangely enough, there seems to be meager information on this point but by no means do I consider myself a student of this phase of medicine. However, I am happy that the question was brought up because of a recent personal incident. This summer, I was asked to participate in a postgraduate seminar at Charleston, S.C. I accepted the invitation, perhaps with some degree of alacrity because I had been rather fascinated by the fact that the first person to point out the relationship between recurrent polyarthritis and heart disease was born in Charleston. William Charles Wells was born in 1757 and practiced there for three years before going to England for further study. In 1810, he cited two cases, a boy of 18 years and a girl of 14 years. The former suffered an attack of polyarthritis at the age of nine years and suffered three later attacks. Following a chill after becoming soaked, he developed severe breathlessness. Dr. Wells pointed out that an uncle of the patient had had a similar type of history and at autopsy had enlargement of the heart. In the case of the girl, there had been bouts of rheumatism and she suffered "violent beating of the heart." He stated she had numerous small tumors along the tendons. After all, American-born observers of classical clinical relationships are not numerous.

Q. You stated that the cause of rheumatic fever is obscure, yet there seems to be much written in support of the so-called streptococcal theory, also of the hereditary feature. Is there a question about these or are other factors more significant?

A. Attempts have been made also to implicate viruses and even Rickettsia. As far as I know, you are correct, the factors you mentioned seem to play the predominant roles. At least from a practical and perhaps not too profound viewpoint we can state the mechanisms involved seem to follow this sequence.

1. Initiating throat infection with hemolytic streptococci, Group A, (one to three days duration).
2. Latent period of one to three weeks. (Army average was 16 days.)
3. Period of rheumatic activity of variable severity and duration.
4. Quiescent period of different lengths with strong likelihood of the development of a recrudescence.

Even though bacteria appear to be involved and a constitutional background (Wilson finds this to be recessive gene pattern) is important and the pathogenesis seems to be such, it has not been determined whether the mechanism is immunologic, chemical or allergic.

Q. Is not the expression "hypersensitivity" often used to explain this disease picture?

A. Yes. At this point it might be well to have a discussion of the evidences of the hypersensitivity aspect. Dr. Fashena has undertaken some investigative work along these lines.

Dr. Fashena: Anyone who embarks on a discussion of hypersensitivity or allergy is well advised to define his terms before going any further. The terminology which is used to describe the various forms of hypersensitivity is as jumbled and confused as anything we have in medicine and has led to a very unfortunate confusion in thinking. When foreign protein, bacterial or otherwise, is introduced into the body, certain changes take place in the tissues which alter the body's reaction to that protein when it is again introduced at a later period. The hypersensitive reactions which may occur vary tremendously in clinical manifestations. They may be so severe as to produce sudden death, or so mild that nothing except a few hives or an itching nose may result. This superficial dissimilarity in the various types of hypersensitive reactions has lead to a complex and confused terminology. However, if one analyzes the various types of reactions, their pathologic and certain of their serologic characteristics, it is possible to distinguish two main catagories of hypersensitive reactions: one, the anaphylactic type of hypersensitivity and the other, the bacterial or tuberculin type of sensitivity. The anaphylactic type, of which anaphylactic shock, the Arthus phenomenon and

probably pollen allergy are all examples, can be brought about by a single parenteral contact with a free antigen or with multiple contacts with small amounts of a similar antigen. It apparently cannot be brought about by parenteral contact with whole bacterial cells or whole viruses. The anaphylactic reaction which occurs when a previously sensitized body is again brought into contact with free antigen, is characterized by prompt, localized, or occasionally generalized edema, by increased vascular permeability, by a tendency toward exudation, by swelling and subsequent degeneration of collagen and in very severe cases by hemorrhage and necrosis. Smooth muscle spasm is also a feature of the anaphylactic type of hypersensitivity. The antibody which is produced in anaphylactic hypersensitivity is often humoral; that is, it can be demonstrated circulating in the blood stream and can be transferred to another individual. When bacterial protein is the offending antigen, an anaphylactically sensitized individual will react to the free antigen, but he will not react to the intact bacterial cells. This has been well demonstrated by Rich and others.

Bacterial or tuberculin type hypersensitivity, on the other hand, is characterized by delayed and prolonged local inflammation in contrast to the prompt reactions which occur when antigen and antibody react in anaphylactic hypersensitivity. The delayed and prolonged reactions of bacterial allergy or hypersensitivity are characterized by local inflammation and by a very marked tendency to necrosis, in contrast to the anaphylactic type, which is only moderately and sometimes not at all necrotizing. The necrosis is usually local, but it can occasionally be a generalized reaction. Bacterial allergy is characterized by the absence of humoral antibody and by the fact that whole bacteria can evoke the hypersensitive response. With these differences in mind, we may now examine the evidence which bears on rheumatic fever.

It has been suspected for a number of years that rheumatic fever represents a hypersensitive reaction of some sort. There are many features of the disease which have suggested this. The close association with streptococcal infection, the free interval between the streptococcal infection and the explosive appearance of rheumatic fever, and the fact that rheumatic fever so strikingly simulates serum sickness in many of its aspects are some of these features. The occurrence of rheumatic skin lesions which are similar to skin lesions in known allergic or hypersensitive states further suggests that hyperensitivity is involved in the rheumatic picture. Attempts have been made to reproduce rheumatic lesions in animals using streptococcal antigens and to demonstrate abnormal antibodies to the streptococcus in human cases of rheumatic fever—all without decisive results. Relatively recently Klinge and Vaubel in Germany and Rich and Gregory in this country have been able to demonstrate that when one induces not bacterial type hypersensitivity, but anaphylactic hypersensitivity by any one of a number of methods, one is able to reproduce lesions which in their location and in their basic histologic characteristics resemble the lesions of rheumatic fever. Regardless of the antigen employed, most workers have been able to reproduce essentially the same type of lesion, characterized by the following: (1) edema and cellular infiltration in the heart valves, (2) focal collections of mononuclear inflammatory cells around the bases of the valves, (3) focal collections of cells in the myocardium, either in blood vessel walls or para-vascular in location, (4) focal necrotizing vascular changes, where a segment of the vessel wall will actually become necrotic, (5) focal necrosis of heart muscle in a few of the animals. All of these are lesions basically similar to the lesions of rheumatic fever, although not identical. Rich and Gregory used horse serum as antigen, while later workers have used egg albumin and human blood plasma fractions as foreign proteins. We have produced similar lesions by injecting anti-rat-heart rabbit serum into rats. Recently Cavelti has demonstrated that a mixture of rat-heart emulsion and killed streptococci, when injected into rats, will produce lesions such as I have described above in a fairly high percentage of animals. The rat-heart emulsion or the streptococci alone produce no change. This worker also reports positive reactions between rheumatic fever sera and human heart antigens by the collodian particle agglutination technic in a high percentage of cases. Attempts to confirm this work in our laboratory on a very small series of cases have yielded a much smaller percentage of positive results.

It must be emphasized that the experimental lesions so far produced do not exactly reproduce human rheumatic fever. Certainly the pathogenesis of rheumatic fever has not been settled by any means. What has been accomplished is the demonstration that the general type of lesions seen in rheumatic fever can be produced in connection with anaphylactic hypersensitivity and that bacterial protein plus organ protein may combine to form an antigenic combination which has properties not possessed by either of its component parts.

Chairman Hansen: For the sake of orientation, we may mention the manifestations of rheumatic fever. We all realize that it is the extreme variability of these manifestations which make it a difficult problem, and that holds not only for the physician but also for the mother. To draw attention to the incidence of the various manifestations encountered in the first attack of rheumatic fever and those in subsequent attacks the following summary is presented.

APPROXIMATE INCIDENCE OF MANIFESTATIONS DURING RHEUMATIC CAREER

Manifestation	*First Attack*	*Subsequent Attack*
1. Pain		
A. Polyarthritis	One-fourth	Two-thirds
B. Mild joint pains	One-fourth	Two-thirds
C. Abdominal*	?	One-eighth
2. Encephalitis	One-fourth	Almost half
3. Nodules	Small	One-sixth
4. Carditis		
A. Cardiac murmur*	One-tenth	Same (?)
B. Marked	Small	Three-fourth
C. With congestive failure	Rare	One-fourth
D. With arthritis and/or chorea	One-sixth	?
5. Skin	Small	One-eighth
6. Nephritis	Rare	Rare
7. General	?	?

* Outstanding symptom or finding.

Dr. A. H. Schoen—Brooklyn: Is it possible that one of the reasons so many cases of rheumatic fever turn up later with heart disease is the fact that we regard the pain of polyarthritis as a major manifestation? Most of the cases have such symptoms as fever, irritability, etc., and come to the pediatrician after having seen several practitioners with no diagnosis made. These cases give us trouble, because they are missed so often in the first attack, turning up later with rheumatic heart disease. Actually, when the mother is questioned there is no history of polyarthritis, but the cases are in cardiac clinics and we can assign no etiology to them.

Chairman Hansen: When I had my training, the one thing which was stressed every time rheumatic fever was mentioned was that the arthritis exhibits redness, swelling, tenderness as well as pain with migratory joint involvement. This was so fixed in my mind that I neglected to consider mild joint symptoms in terms of rheumatic infection. When the classic joint features are present, the clinical diagnosis is clear cut. One should, however, take time to examine the joints of those children complaining of minor pain for slight swelling, tenderness and even local heat. There are other features in regard to mild joint pains, but we must pay attention to minor or mild manifestations and we must train mothers also to pay attention to them.

Dr. G. R. Fisher—Denver: Our problem is rapidly getting to be the ruling out of a diagnosis of rheumatic fever instead of ruling it in. The doctors diagnose rheumatic fever, based on the story that the children had a mild attack of joint pains. The entire treatment of that child in the future depends on the accuracy of the diagnosis of the disease, and with this situation our experience is going to increase.

Dr. H. C. Graham—Tulsa: What are the minimal symptoms that will ultimately result in a diagnosis of rheumatic fever. We see children with mild, indefinite, obscure symptoms which occasionally may suggest a diagnosis of rheumatism. Such symptoms ultimately turn out to be rheumatic fever.

Dr. R. N. Andrews—Mankato, Minn.: When these borderline cases have a little fever, practically no other findings, and the tonsils are moderately infected, what is your method of handling them?

Chairman Hansen: It is a matter of regret that there is no simple way to prove the presence of rheumatic fever. The diagnosis is made solely on clinical grounds. We must rely on a complete and accurate history, a thorough physical examination, laboratory data, plus the ever-important knowledge of the basic features of the disease itself. I have found that a diagnosis is facilitated by marking as positive or negative various points from the history, physical examination and laboratory data in a manner listed below:

DIAGNOSIS OF RHEUMATIC FEVER ATTACK

A. History

Pain: Extremities, abdomen, chest.

1. Symptoms:
   Joints: Swelling, redness, tenderness.
   Nervousness or irritability.
   Cardiac: Dyspnea, cyanosis, edema.
   Skin: Erythema.
   General: Epistaxis, anorexia, weight loss, pallor, fatiguability, palpitation, fever, frequent sore throats.
2. Past: Previous attacks, initial sore throat.
3. Family: Immediate, related.

B. Physical Examination

1. Appearance: Malnutrition, pallor, edema, nervousness, emotional status, muscle control, nodules.
2. Cardiac: Size, rate, pulsations, thrills, tone, murmurs, rub.
3. General: Blood pressure, weight, fundi, temperature.

C. Laboratory:

Hemoglobin, white blood count, differential, Urine.
Sedimentation Rate
X-ray (Size, configuration)
ECG
Vital capacity, venous pressure
Blood culture, metabolites
Biopsy (if indicated)
Weltman reaction

It is the physician alone who has the necessary background to interpret these data. Incidently, this indicates that whatever type public health program is made up to control rheumatic fever, the physician is the key individual.

The fact that we have no specific laboratory tests for rheumatic fever does not imply that laboratory information is not extremely valuable in diagnosis. Dr. Fashena will summarize some of the useful laboratory findings.

Dr. Fashena: As far as hematologic studies are concerned, most rheumatic fever patients have a mild secondary anemia, not nearly so marked as one might expect from the washed-out appearance they present. Although one reads in text books that leukocytosis is characteristic of an acute attack of rheumatic fever, it has been our experience that an elevated white blood cell count, if present at all, is usually present only in the first week or two of the active disease. In this period, a majority of patients will show a moderate elevation of the total white blood cell count, with some

left shift in the hemogram. When seen after this period many patients exhibit normal total and differential white blood cell counts in the presence of undoubted active rheumatic fever. In the border-line cases of rheumatic infection this is even more true. As far as the urine is concerned, again, there is nothing specific or even characteristic. A fair number of these patients will have few red blood cells in the urine if the sediment is carefully examined. The test for albumin is usually negative.

The erythrocyte sedimentation rate has been emphasized a great deal by many people, and we think it is helpful in a good number of cases, though by no means diagnostic. When the test is set up immediately after the blood is drawn, the ESR is elevated in the majority of patients during the acute stage of the disease and is usually quite markedly elevated. However, we have observed patients with enlarging hearts and changing murmurs who have had undoubted active rheumatic fever where the ESR was entirely normal. It is also important to remember that the ESR may abruptly drop to normal when cardiac failure supervenes. Conversely, you have all seen many patients who have exhibited all degrees of elevation of the ESR who were later found to have some infection other than rheumatic fever. One may then occasionally encounter acute rheumatic fever without elevation of the ESR and one may certainly have elevation of the ESR and not have rheumatic fever.

A word might be interposed here about the bacteriologic aspects of diagnosis. A number of people seem to feel that the finding of hemolytic streptococci in the throat is a helpful point in diagnosis. In a bacteriologic survey of 175 well children in the Dallas area we found that 20% of the children, on a single throat culture, showed the presence of Group A beta hemolytic streptococci. This makes me feel that the diagnostic import of a positive culture for hemolytic streptococci is relatively slight. The next item on the list is X-ray. Fluoroscopic and X-ray examination of the heart is of some help in deciding whether a patient has rheumatic carditis; it is not diagnostic of acute rheumatic fever. In patients who have acute rheumatic fever with carditis, one is able to detect cardiac enlargement in a considerable number. The P-A 6 foot X-ray film is a poor way to make this examination in my opinion because one has to have considerable cardiac enlargement before it shows up in this view. A better way is fluoroscopic examination, with a barium swallow, in the oblique as well as the P-A positions. One of the first changes to occur in these patients is left auricular enlargement and this can be seen earliest in the right anterior oblique view with the help of a barium swallow. There are other rheumatic manifestations in which roentgenograms are helpful,—pneumonitis, pericarditis with effusion, etc.

As far as other indications of cardiac involvement are concerned, I consider the determination of vital capacity a sensitive test to indicate the presence of carditis. It is often equivocal, however, in acute rheumatic fever without evident carditis. Electrocardiographic examination may also furnish evidence of the presence of active carditis in acute rheumatic fever. The frequency of positive findings on electrocardiograms is in proportion to the number of tracings taken. If one takes an electrocardiogram every day or so for a period of weeks or months, as was done at Duke University, one finds a very high percentage of electrocardiographic abnormalities at one time or another—over 80%. If only one or two tracings are obtained, one commonly misses the evanescent changes. The abnormalities which are usually found and which are said to be characteristic of acute rheumatic carditis are: (1) prolongation of the A-V conduction time, which is mirrored in prolongation of the PR interval, (2) changes in the RT segment and in the T waves, particularly in lead IV, (3) notching and slurring of the QRS complexes, and finally, (4) something which has been described by Taran and which we have found rather helpful—prolongation of the QT interval, or the duration of electric systole. Taran has found that practically all patients with acute carditis showed QT intervals which were over 0.41 seconds; whereas, his normal controls were in every instance under 0.41 seconds. We have had no experience with the Weltman reaction, so I am unable to comment on its usefulness as a diagnostic test.

Chairman Hansen: We may continue the discussion on differential diagnosis of rheumatic fever, because after all diagnosis involves consideration of the differential diagnosis. There are listed on the chart such things as blood cultures. If the blood culture is positive for a particular organism, there is no worry about rheumatic fever. Repeated negative blood cultures may sometimes be very helpful. If you have subcutaneous fibroid nodules there is very little else other than rheumatic infection that can be considered. There are many features of rheumatic fever which can be simulated by other

diseases. I published an article in the J.A.M.A. (121:987, 1943), discussing the question of differential diagnosis. I found in going over many textbooks, periodicals and lecture notes that a large number of diseases—some 50 to 60 different conditions were found—are mentioned that might be confused with rheumatic fever, far beyond the point of being practical even in trying to remember. We studied 350 children who were sent to the clinic, most of whom had been sent by practicing physicians. The referring diagnosis was given in their notation. If the patient had arthritis and a heart murmur we assumed he meant rheumatic fever. When we studied the problem from this approach we found that about two-thirds of these cases were diagnosed quite readily. We had the advantage of being able to follow them over a period of time and, therefore, were in a little better position to make an accurate diagnosis. We also approached the question of diagnosis from the viewpoint of how many children during a given year have rheumatic fever given as a diagnosis in the referral letter and subsequently the condition turns out to be otherwise. For instance, when Sister Kenny was carrying on her campaign for early treatment of polio, it was surprising to see the number of children who were sent in for treatment for polio—only to find they had rheumatic fever. Our studies showed about 3% of the children had rheumatic fever mentioned as the admitting diagnosis. If we considered children of school age and excluded such conditions as diabetes, fractures and a number of other things with which there was not much likelihood of confusion, we found in about 10% of the cases rheumatic fever was considered in the differential diagnosis.

In summary, from these studies we could say that in two-thirds of the cases diagnosis was relatively easy. In about one-fourth the diagnosis was difficult. In one-third of those, pain was a prominent feature and in about one-fourth of this group the diagnosis was some phase of appendicitis—ruptured or recurring. When we broke these observations down, the results shown in the following chart were obtained:

Pain, Fever, Etc.

Appendicitis
Poliomyelitis
Osteomyelitis
Nephritis
Leukemia
Hodgkin's disease
Rheumatoid arthritis
Sickle cell anemia
Meningococcemia

Nervous or Chorea-like Symptoms

Hyperthyroidism
Emotional problems

Acute Fulminating Illness

Bacterial endocarditis
Sepsis
Pneumonia

Skin Eruption

Erythemic disorders
Purpura

Low Grade Infections

Dr. Andrews: When all symptoms have subsided in a case of rheumatic fever, but ESR is still increased, what is your method of determining whether to keep the child in bed?

Dr. Fashena: That's a hard question to answer! If a patient appears to be well, has no clinical or laboratory evidence of active disease, and the ESR is still very significantly elevated, some type of activity is still in progress. The first thing to do is to look for evidence of other infections, check the tuberculin reaction, take multiple X-rays, etc. If nothing else is found and the ESR persists in being markedly elevated, such a child should continue to remain at bed rest. If the ESR is only mildly elevated, however, it may not portend activity. Let's say that it has fallen from 100 to somewhere around 20 or 25 mm., and there it stops. After a reasonable period of observation to be sure that the child's ESR is not going to fall any further and taking into consideration the presence or absence of anemia, which in itself may be responsible for the increase in ESR, it is permissible to allow such a patient some activity very cautiously, following him very carefully from a number of standpoints: fever, pulse rate, ESR to see if it rises any further, cardiac status, and so on. If, on allowing such a patient limited activity no evidences of rheumatic reactivation occur, we cautiously expand his program. We have one or two patients who have been restored to full ambulatory status

who have carried their ESR at about 20 to 25 mm. without any evidence that they had any active disease. That may be the wrong thing to do, but I am very much convinced that one does harm in keeping children in bed indefinitely. I'd rather take the the chance of some reactivation than to make a chronic invalid out of a patient who really has nothing the matter with him. I admit it's a compromise, but it's the best one I've been able to arrive at.

Dr. B. P. York—Houston: I'd like to ask Dr. Fashena if she has compared the micro ESR rate with the standard method.

Dr. Fashena: Only in rats, not in humans. I am sorry that I can not answer that. I can tell you, however, that Dr. Carl Smith in New York has done a lot of work with the micro ESR and feels that it is just as reliable as the macro procedure, perhaps even a little more so.

Dr. H. W. Elghammer—Chicago: We have seen many of these patients with high sedimentation rates, which is pronounced as a bad sign, whose rates would suddenly become normal or even subnormal. This has usually happened just before cardiac failure occurred and here it seemed that a fall of ESR was a bad instead of a good sign.

Dr. Fashena: I'm glad you brought that up. It was mentioned when discussing the ESR, but probably not sufficiently emphasized. It is well documented that one of the earliest signs of impending cardiac failure in a patient with active rheumatic fever is a sudden drop of the ESR to normal or even below normal. I don't know what the mechanism is. In the presence of any signs of cardiac failure or just before cardiac failure supervenes the ESR means absolutely nothing unless it means that failure is going to occur. Another circumstance which may falsely lower the ESR is the administration of large doses of salicylates. This has been demonstrated *in vivo* and *in vitro.*

Dr. Elghammer: What is cardiac failure in the rheumatic fever child—it occurs at the height of infection, and the liver enlarges prior to failure of the heart. Are we dealing with rheumatic infection of the liver? Pneumonitis also occurs at the beginning of cardiac failure. Does the infection become fulminating in the liver, the lung and the heart? The failure then is not due entirely to myocardial injury, but to the generalized infection. Does the change in the ESR depend on disturbed liver function?

Dr. Fashena: I wish I could answer your questions—I'd know a lot more than I now know if I could! There are two schools of thought about the etiology of liver enlargement in acute rheumatic fever. You all are familiar with the fact that a picture which appears to be right sided cardiac failure occurs in a certain number of patients who have severe, acute rheumatic fever. These patients usually have a large, tender liver which may be one of the first manifestations, and they also frequently show sudden cardiac enlargement, a gallop rhythm, a very much more rapid cardiac rate and elevated venous pressure, increased circulation time, and so on. There are those who believe that the enlargement and tenderness of the liver are not dependent on right sided failure, but are manifestations of the acute rheumatic process itself. I happen to belong to the other school of thought. In my experience these large tender livers appeared to be the result of right sided congestive failure. Almost invariably at the time when we see these patients, they not only have a large liver but also some elevation of their venous pressure and other evidences pointing to right sided cardiac failure.

Dr. J. F. Sander—East Lansing, Mich.: In communities where rheumatic fever is prevalent the lay population is often more conscious of it than the medical profession. It has been pointed out this morning that a diagnosis of rheumatic fever is made occasionally on negative findings. Frequently a child with a low grade pyrexia, a body temperature of 37.2° to 38° C. is seen at various times during the day. The laboratory, X-ray and electrocardiograph examinations are entirely negative, and the other clinical findings are also negative—usually with increase in fatigability and always in my experience, increase in irritability. These patients are troublesome and the problem is hard to handle. Are we justified, then, in making a clinical diagnosis of rheumatic fever?

Chairman Hansen: It is a mistake to make a diagnosis of rheumatic fever on any particular day. If there is any suspicion of rheumatic fever, the patient should be followed until ultimately you

will be able to make a correct diagnosis. We should not depend upon the specific information at one time, but must know over a period of time what happens.

Dr. Sander: The difficulty is that the diagnosis is made by the parents before we see the patient, through the help of the magazines, and it is up to us, as physicians, to confirm or refute the premade diagnosis.

Dr. Vivian Tappan—Tucson, Ariz.: May I stress certain aspects of the diagnosis of the questionable cases of rheumatic infection, because an increasing number of cases as you have described are being sent to physicians with partial diagnosis. Not only do they come with a questionable diagnosis, but the problem of when to let the children up or what activity to permit them has become a nightmare. Is the sedimentation rate the one and only criterion of active rheumatic infection? I have seen children made helpless invalids—not for months, but for years—because of a slightly elevated sedimentation rate. In that case I do not make a diagnosis of rheumatic infection. The diagnosis can be withheld, classifying the child as a possible, potential, or probable rheumatic infection case. He can be guarded in every way without making a final diagnosis. If the child once has the diagnosis of rheumatic infection made by competent individuals, it will follow the rest of his life, and may handicap him in industrial and social life. I should like to make a plea for the consideration of active rheumatic infection in the child as a whole not in any one part alone. Actually, the type of child about whom the doctor is talking with fever, irritability and fatigue may have any one of the group of diseases Dr. Hansen described. The responsibility of a doctor should be toward education of the parents and through the parents of the community in the fact that we do not necessarily know at any one time what causes unexplained fever. There are other diseases associated with a low grade fever and you have mentioned also irritability and fatigue. The same low grade fever in a healthy individual won't bother nearly as much unless you have these additional factors. Certain children will have a low grade fever in the afternoon, and the question then becomes "is this real fever." I have these children rest to see how much and how rapidly the temperature falls. A rectal thermometer always should be used to determine whether fever is present. I determine whether a temperature will drop to physiologic levels. One should determine the daily span of temperature, whether it is between 0.5° or 1.0° C. or whether in the morning there is a marked drop and in the afternoon a higher level. If you are going to have children with borderline unexplained fever, you must withhold the diagnosis and not make it on the basis of vague signs. Emotional factors such as visiting days in hospitals have demonstrated that on those days there is a slight elevation of temperature which does not occur during the week. One may say that the body temperature in healthy individuals is less likely to do that, but it is well known that healthy individuals may have significantly elevated temperatures which drop immediately. I should also like to add one word about the helpfulness of serial X-ray, if one can afford to take them. The normal range of the shadow of heart size is extremely wide, and the significant change in serial X-rays on the same child may be important. The position of the diaphragm will give totally false concepts of the change in size of the heart in the same individual. One should try to repeat the exact position of the diaphragm in the earlier position.

Dr. B. Hoyer—Cincinnati: Our educational program should include the education of physicians as to how to diagnose rheumatic fever, but also we can educate the public on what to expect from the physician. Let the public understand what we can be sure of and what can be done. I have read nothing in the literature that tells the public we are limited in our knowledge and in our ability to make the diagnosis. The sooner we begin to educate people as to what they can expect, the sooner we will get to the solution. We have had that experience in Cincinnati about appendicitis. The mortality rate in appendicitis was extremely high some ten years ago, the highest in a group of 13 cities. People were educated to bring patients to the hospital when they had an abdominal pain, but they were told also that abdominal pain need not mean appendicitis necessarily, and our mortality rate has dropped considerably to a point we may boast about—just by educating the people; and that included everybody. Our program took in druggists to have them avoid selling drugs to relieve abdominal pain. The whole community was educated in the problem of appendicitis; just what they might expect from the doctor—and the limitations of the doctor.

Chairman Hansen: We are not in a position to present the whole story of rheumatic fever. The problem is tremendous, and is one for the whole community. We can talk here about diagnosis and

the management from the viewpoint of the physician because a good part of our difficulty is that we are not well acquainted with the problem. That is partly because of the nature of the disease itself, and we should not feel compelled to prove or disprove a diagnosis of rheumatic fever at a particular time. Appendicitis—Yes; we state we are going to solve that problem: we have to diagnose that disease and operate. But the same thing will not hold true for rheumatic fever. I thoroughly agree that education should be from the physician. Our discussion has deviated from the diagnosis and differential diagnosis to the matter of the course of the disease and management of the disease in the various stages.

Course

Both from the viewpoint of rendering a prognosis, as well as management of the patient, knowledge of the course of the disease is valuable. It is impossible to predict the duration or intensity of symptoms which may occur in any given attack. We must bear in mind that the shorter attacks are several weeks in duration, and that some attacks persist for several years with varying intensity. Gibson and Denenholz (J. Pediat. 9:505, 1936) found the duration to be less than three months in only one-fourth of their cases. In recent years, we are more aware than ever that pathologic evidence of activity exists long after all clinical evidences seem to have disappeared.

It is my firm belief that we should think of rheumatic fever only in the terms of years and decades. I am inclined to use the expression, "rheumatic career." This, of course, because the quintescence of rheumatic fever is its propensity for repeated attacks, called recurrences, recrudescences or flare-ups. This subject was covered in some detail in the American Academy of Pediatrics two years ago and was published subsequently (J. Pediat., 28:296, 1946). Therefore, we will not devote any particular time to this, now.

Q. Which points regarding recrudescences do you think we should keep in mind?

A. The majority of children with rheumatic fever will have a recurrence. This is especially likely to develop before the ages of 15 or 16 years. The more recent the acute attack, the more apt is the recrudescence to develop. The majority of recrudescences develop within five years after any attack.

Prognosis

This brings us to the consideration of some of the details for the outlook of the disease. Available data indicates, for example, that in large groups during a 10 to 20 year period, somewhat less than one-third (20 to 35%) of the children will be dead; somewhat more than one-third (40%) will have cardiac damage of some degree; and less than one-third (20% to 30%) will have complete recovery.

Q. At what age are children particularly apt to die from rheumatic infection?

A. As far as the childhood age group is concerned, they are more apt to die between 10 and 15 years of age. These are peak years of rheumatic activity and this brings to mind comment that the greatest portion of children die from acute rheumatic activity. If the individuals survive the childhood period, the dangerous period is up to 40 years of age. Coombs found the average age of death to be 28 years. Incidentally, it is stated also, that less than 1% die in the first attack.

Q. Is rheumatic infection apt to carry a graver prognosis when the patient is very young at the onset?

A. That seems to be the usual opinion. However, some authors will not confirm this.

Q. Would you make a more guarded prognosis, if the child had an intensive polyarthritis?

A. The significant features which seem to affect the prognosis are the presence or absence of carditis. We must remember that patients having chorea alone have a better prognosis.

Q. Are there any special manifestations which you consider as "red lights" in giving a prognosis?

A. The features which seem to be significant are: (1) presence of rheumatic nodules indicates graver outlook, (2) congestive heart failure as part of an attack carries a continuously graver ultimate outcome, (3) eliciting of a friction rub as a sign of pericarditis is associated with the more severe cases, (4) auricular fibrillation is more apt to develop in the cases with a severe prognosis, and (5) the number of attacks has added significance. At this point, we cannot

help but emphasize that we must be just as cautious in managing the child with mild manifestations as with the child with severe manifestations.

Q. What manner of death occurs in children with rheumatic affliction?

A. The majority of children who die of rheumatic fever die of congestive heart failure. This results from activity of the disease. Recent work indicates that even in the young adult group decompensation is apt to be associated with a flare-up of the rheumatic involvement. Only a small portion of children suffer the chronic heart failure resulting from mechanical defect of the valves. Subacute bacteria endocarditis occurs less frequently in the younger than in the older or adolescent child. We must also be alert to the possibility of development of acute endocarditis. One thing pediatricians should bear in mind is that in those children who have had severe rheumatic infection sudden death occurs occasionally. Estimates are made that from 2% to 5% of the cases succumb in this manner.

Q. We have been told previously that the ultimate prognosis with aortic regurgitation is better than with mitral stenosis.

A. During the childhood period this does not seem to be as significant as a guiding feature as it is in later decades.

Q. Does adhesive pericarditis carry a poor outlook?

A. This is difficult to determine as the incidence in the series of rheumatic fever is small. After all, chronic constrictive pericarditis is not frequent. However, it has been stated in those patients under 21 years with this condition, almost one-half are considered to have been on a rheumatic basis.

Q. How long should one give an extremely favorable prognosis in the event that one finds no murmur within a three year period following an acute rheumatic episode?

A. If one could guarantee that the best prophylactic measures will be carried out, one could feel indeed encouraged. However, we must have a certain grim attitude because in a number of instances, some say as high as 10% to 25%, only 10 to 15 years later is definite valve damage discernable.

Before we close this discussion of prognosis, of which there is much more to say, we cannot help but mention certain features of which we know all too little. That is—the late sequelae: Bruetsch has pointed out the greater incidence of rheumatic fever in institutions for patients with mental disease; Foster has stated that convulsive episodes also have a greater incidence in patients with rheumatic background; Taussig and Hecht have pointed out the possibility of hypertension following rheumatic involvement (Bull. John Hopkins Hosp., **62**:491, 1938). We must bear in mind that occasionally patients who have had chorea (that is, certain ones) may develop a chorea of pregnancy. One feature of prognosis about which we are very ignorant is to what extent ultimate prognosis is influenced by various types of regimens. For example, climatic change, dietary, social, supervised convalescent care and sulfonamide prophylaxis.

Management

Before we go into details of treatment, it appears worthwhile perhaps to re-emphasize the significance of activity of rheumatic infection. So many of us, and I've noted this often times of students, when speaking of rheumatic fever, ask the question, "What is the sedimentation rate?" True enough, this test is valuable and is perhaps the most singularly valuable of all. Nonetheless the "activity of the infection" should be made on the basis of all clinical data. Rather than duplicating the chart which was presented under "diagnosis," we could simply use the same outline or scheme presented there: the positive, or plus sign, indicates presence of rheumatic activity, and the negative or minus sign, reveals evidence of the quiescent phase. Hence, we must think of the management of rheumatic fever in the terms of the stage of rheumatic activity and the stage of quiescence. Before Dr. Fashena discusses the management in the acute phase, we will outline briefly, the overall aspects of the management of treatment in the terms of: acute phase, subsiding phase, convalescent

phase and quiescent phase. Again, let us recall, that rheumatic fever in children should be thought of as a "career" rather than as an incident. Dr. Fashena will now discuss the treatment in the active or acute stage.

Dr. Fashena: The remarks to be made now apply to patients in whom the diagnosis of active rheumatic fever is definitely made. I don't mean to imply that these steps should be taken in doubtful cases. If you have a patient who has undoubted, definite, active rheumatic fever, it is my belief that one of the very important parts of his treatment is complete bed rest, in spite of the fact that there's quite a vogue these days in the opposite direction. One should try to put the heart at as nearly physiologic rest as is possible. If he is very ill, the child should have no bathroom privileges, should not be allowed to feed himself and so on. Many times it is necessary to use sedation to accomplish this end. For older children with severe carditis, we occasionally use morphine in a dosage of 1 mg./5 kg. body weight. In the vast majority of instances, the barbiturates are used for sedation. Diet is a very important part of the treatment, and one which is very neglected. Many of these patients don't eat very much—they're not hungry—particularly those who have carditis. It's an effort for them to eat and it's quite important, I think, to give them appetizing food and to try to increase their protein intake by giving them highly concentrated protein mixtures, using something like Protenum or some other palatable protein concentrate. A complete supplement of vitamins is routinely prescribed. Our practice is to use two or three times the amount considered to be the average daily requirement since we know that vitamin metabolism is disturbed to some extent in chronic infections.

It has been our practice to use oxygen for all severely ill, rheumatic fever patients with carditis, whether or not they exhibit evidence of cardiac failure. It has been well demonstrated by Poulton in England and by Barach and Taran in this country that one obtains excellent results by the use of a very high oxygen atmosphere. Such treatment appears to make these patients very much more comfortable and in many instances their cardiac rate decreases appreciably. In some instances it seems to shorten the course of the illness, also to lessen the number of permanent cardiac residua.

The use of massive salicylate therapy for rheumatic fever is a controversial subject. It has been known for over 50 years that salicylates are very excellent medicaments for the treatment of the exudative and febrile manifestations of the disease, but few considered the drug of benefit in stopping the proliferative manifestations of the rheumatic process. As you all know, in 1943 Dr. Coburn published a paper reporting that if one gives massive salicylate therapy and particularly if one gives it intravenously (doses for adults ranged from 10 to 20 gm./day of sodium salicylate), one can inhibit the proliferative manifestations of the disease. He reported a very impressive series of patients in support of his thesis. This startled everybody a good deal and a number of different people started working with massive therapy in the hope that they could reproduce his results. A confirmatory report was made by Taran who states that if he is able to start treatment with massive salicylate therapy on a patient very early in the course of his first attack he is able to shorten the course of the disease and also to reduce the amount of residual cardiac damage.

On the other hand, there have been unfavorable reports in the literature on this type of treatment. Wegria has tried the Coburn treatment on a group of cases and was unable to detect any differences between his treated cases and his control cases. He does make the point, however, that in no instance was he able to treat an individual who had been ill for one week or less and it may be that this therapy does prevent the proliferative manifestations of the disease if it is given at the very onset of the attack. Our experience has been much along the line of Wegria's; we have been unable to detect any significant difference in patients treated by massive salicylate therapy and we also have had some very unfortunate experiences with this mode of therapy. As the result of a good deal of the work on the subject of salicylate intoxication, we are convinced that children are much more susceptible to the toxic effects of salicylate than are adults. Coburn states that one has to achieve a blood level of salicylate somewhere in the neighborhood of 35 to 40 mg./100 cc. blood in order to produce optimum therapeutic results in rheumatic fever. To achieve these levels it is necessary to administer somewhere between 0.2 and 0.3 gm./kg. body weight of salicylate per 24 hours. We have been unable to obtain the necessary levels with anything less than these doses and in some instances it has been necessary to use 0.4 gm./kg. body weight of salicylates. It has been our unfortunate experience that almost invariably when we achieve salicyl levels of 35 to 40 mg./100 cc. blood we also elicit the early toxic manifestations of salicylism which are nausea

vomiting, tinnitus, and hyperpnea. In a series of 50 patients treated in this way, all except two have shown two or more of the toxic manifestations noted above when the blood levels reached 35 to 40 mg/100 cc. blood. Taran states that nausea and vomiting are not contraindications to continuation of therapy, but I can not be convinced that a child who has acute carditis and who is severely ill is benefited by vomiting everything he takes by mouth over a period of days or weeks. Therefore, in our hands, it has been difficult to use massive salicylate therapy in any significant number of patients with rheumatic fever. The later manifestations of salicylism are excitement to the point of delirium, hypoprothrombinemia (this may occur very early and with very small doses in some individuals), marked hyperpnea which is centrally initiated, and which may lead at first to a respiratory alkalosis, marked metabolic acidosis because of the effects of salicylate on certain enzyme systems and also because of base depletion incident to excretion, and finally coma, hemorrhages and death. We have actually observed one rheumatic patient who on another hospital service developed these severe signs of salicylate intoxication and died. One can control the hypoprothrombinemic tendency of salicylate by the use of vitamin K and occasionally also the use of vitamin C, but one can not control the centrally initiated hyperpnea and the nausea and vomiting in any way that I know. Even if the drug is given intravenously nausea and vomiting occur and in our experience the toxic symptoms have been parallel with the blood level, regardless of the type of salicylate preparation used. In patients who are in danger of developing cardiac failure, if one gives sodium salicylate or aspirin plus soda bicarbonate, one increases the sodium load tremendously and often precipitates frank cardiac failure. Taran has stated that his toxic manifestations from massive salicylate therapy have been minimal but this has simply not been our experience. We do, of course, use salicylates as symptomatic treatment. I know of nothing better for the relief of joint pain and lowering of temperature, and we consider it important to bring down fever because of the usual concomitant lowering of the cardiac rate.

In 1945 a report appeared claiming excellent therapeutic results for the use of succinic acid benzyl ester in rheumatic fever. A very recent report makes similar claims for para-amino benzoic acid. Both of these reports lack confirmation.

I do want to say a few words about the treatment of cardiac failure when it occurs during the active stage of rheumatic fever. It is generally conceded, I believe, that cardiac failure occurring in a rheumatic patient in the pediatric age group bespeaks concomitant active rheumatic carditis. These patients should be treated very much the way all people with cardiac failure are treated, bearing in mind that when you use digitalis you don't expect to get particularly good results. We put such patients on a very low sodium intake (less than 500 mg. of sodium per day) and we do not restrict their fluids. It has been shown very well by Schemm and others that what one really needs is sodium restriction and not fluid restriction. The patients are given continuous oxygen therapy and are treated with diuretics, using xanthine diuretics such as theocalcin first, and resorting to mercurial diuretics if the xanthines prove ineffective. If these measures fail to produce the desired result, we then use digitalis, realizing that it is not too effective in active carditis. There are some people who feel that digitalis should never be used in acute carditis because some of the toxic manifestations of digitalis are the same as the injurious effects of rheumatic fever on the heart itself. However, Gold believes that the indication for digitalis therapy is cardiac failure whether or not myocarditis is present, and we have used it many times in patients with active rheumatic carditis, occasionally with very satisfactory therapeutic results. We use either powdered leaf in the dosage of 0.3 cat unit/kg. body weight of digitoxin in the dosage of 0.02 mg./kg. body weight for a full digitalizing dose. The digitalizing dose is usually split and is administered over a 24 to 48 hour period, and the patient is always examined carefully before each dose is given. Daily and sometimes twice daily electrocardiograms are taken. One of the best indications of full digitalis effect appears to be the T wave flattening which occurs. Sometimes digitalis does not produce any very striking results but we have seen no instances where the drug actually appeared to do harm. We have not seen any deaths which were thought to be due to digitalis, nor have we seen heart block develop. Just a word about chorea—we use heavy sedation with barbiturates and bed rest, just as everyone else does. I haven't seen any miraculous cures from fever therapy, but I think it does shorten the course of the disease somewhat. I know of nothing else for chorea.

Chairman Hansen: Another difficult question is whether chorea can be due to rheumatic fever. About one-fourth of the cases of chorea are supposed to be idiopathic.

Dr. Fasbena: We have followed 18 cases where the onset was with chorea without any other manifestations and without carditis. After nine years now, 70% of them have cardiac lesions!

Chairman Hansen: What would you say the figure would be if you followed them for another nine or ten years?

Dr. Fasbena: I don't know.

Subsiding Phase

Chairman Hansen: Q. The feature which characterizes the subsiding phase is that most of the children are remarkably comfortable. Yet one knows they should be given the benefit of bed rest. But, how long?

A. The primary objective during this phase is to continue rest in bed. The optimum duration of this period, in order that the child may have the utmost benefit and yet remain satisfied, is difficult to determine. Each case must be individualized, but certainly the safest rule to follow is to wait until all signs of rheumatic infection have disappeared before the patient gradually is allowed to assume normal physical activity. Often, the ingenuity of the parents or nurse is taxed to capacity to keep the patient occupied during this recovery phase. In certain localities "stay-in-bed" clubs may be organized to help keep these children happy. In addition to use of the library for books, it may be possible to have a toy library from which different toys may be borrowed for short intervals. Occupational and play therapy are very important, but emphasis should be on such occupational therapy as can be done in bed without demanding physical exertion or causing excitement. Such devices as mechanical supports for books while reading and suspension of toys from frames above the bed will relieve physical strain while the child is being entertained. When the rheumatic fever activity has subsided, gradual resumption of physical exertion may be instituted in accordance with the routines usually prescribed.

Q. In other words, there is no rule?

A. Right, this again depends upon clinical judgment in the present state of our knowledge. I might add, however, that during this stage, we should pay attention to supplying the right diet with vitamin supplements and iron. Occasionally, it is necessary to give small blood transfusions to correct the tendency toward anemia.

Convalescent Care

Actually, to define convalescence is rather difficult, but we might assume this begins when all signs of rheumatic infection have disappeared, and ends when recovery is complete with full resumption of physical activity. Strictly speaking, we should consider this to be until undisputed quiescence has been obtained. This period is indeed variable. In some instances, one to two months; others, one to two years. As an average, we should think of it as four to six months.

On this occasion, I do not feel we should debate the merits of individual home convalescence in contrast to well-supervised convalescent homes. As we stated earlier, the communal and social aspects of the rheumatic fever problem should be thoroughly outlined and discussed. It is here that details of institutional convalescent care should be presented. However, this is beyond our province. We assume, then, that insofar as we are concerned our discussion is directed by the individual physician for the individual child. It should be borne in mind that far more disastrous results occur because of reactivation of the rheumatic infection than result from excessive physical activity. Nevertheless, caution should be the rule, and it is better to advise a few weeks of extra quiet than to allow strenuous activity too early. In principle, it is better to state in a positive manner the type, kind and time of activity allowed rather than to list limitations and "do nots." A routine which may be planned and has often worked out satisfactorily is presented here in very brief outline form. The introduction of each new type of activity should be separated from one-half to one week in those patients with little or no evidence of carditis and from one to two or even three weeks where there has been cardiac involvement:

Patient allowed to hold book, 15 to 30 minutes, two to three times a day.
Feed self; mild play activities.

Sit up in bed (propped with pillows at first) for 15 to 30 minutes; first once, then twice daily, for one to two weeks; then back rest for longer intervals.
Bathroom privileges, first being carried, once, then several times daily for one to two weeks; gradually increased and walking allowed.
More extensive occupational therapy.
Up-in-chair privileges, 15 minutes once daily; then twice and gradually increased.
Rest on porch or in garden; sunbaths.
Meals with family; first dinner, then lunch, then breakfast.
Walk about the house 15 minutes once daily, then twice, then for 30 minutes two or three times a day.
Out-of-door walking on level ground, few minutes daily; later 15 minutes.
Out-of-door walking 15 to 30 minutes twice daily for one to two weeks.
Begin limited school work at home.
Climb stairs slowly just once daily; then several times.
Mild play activity 15 to 30 minutes daily.
Gradual resumption of more activity but with continuation of rest period in the morning for one hour and in the afternoon for two hours, and going to bed immediately after the evening meal.

Such a schedule may be organized to cover a two to four month interval or even more, and later just an afternoon rest period may suffice. Resumption of school activities should begin with only one to two hours at school each day for a few weeks; then a full half day schedule; and finally the full day with continuation of rest period of two hours after school and preferably an additional rest hour at noon in school. It is impossible to set up schedules that apply to all children, as each child must be individualized in this regard. The physician should evaluate the child's condition at two to four-week intervals to detect evidences of activity of the rheumatic infection as well as to ascertain the effect of increasing physical activity. In those children who have had no signs of carditis, this whole schedule may be compressed into a six to eight week interval. On the other hand, for those who have had severe carditis, especially signs of cardiac failure, the whole may be expanded to occupy even a period of one to two years.

Q. You have failed to mention the removal of tonsils.

A. Rightly so, if there are real indications, independent of the rheumatic fever for removal of tonsils, it should be done. Removal of the tonsils and adenoids should be undertaken only if indications such as frequent sore throats, peritonsillar abscess, marked cervical adenitis, or otitis media have been present. It should be borne in mind that removal of tonsils per se will not affect the course of a rheumatic infection nor prevent recurrence of the infection; thus, removal should be on the basis of findings independent of rheumatic fever. When infected teeth are removed or tonsillectomy or adenoidectomy performed, it is well to administer sulfonamides as a prophylactic measure to prevent a flare-up of the rheumatic infection. For this, sulfamerazine or sulfadiazine may be used, 1.0 to 2.0 gm. daily, and continued for about ten days. The usual precautions for any sulfonamide administration should be followed and urine examinations, hemoglobin determinations and leucocyte and differential counts should be made regularly. Penicillin also is used prophylactically and seems especially indicated in the removal of infected teeth in preventing development of subacute bacterial endocarditis.

Q. Often we hear the expression, "healthful living conditions." What is meant by that at this stage of the disease?

A. It is my belief that this means nothing more than the simulation of the theoretical idyllic state, which means plenty of sunshine, fresh air, nutritious diet and freedom from worry—easier said than done, in many instances.

Q. So many times, the parents of my patients are almost panic-stricken then, of course, the poor kiddies develop distinct behavior problems. Do you think we are neglecting our jobs by not warning against the possibility of anxiety states?

A. Rightfully so, we should make it a point to warn against an induced invalidism. While it is recognized that fatigue and excessive exercise in the rheumatic fever patient should not be

permitted, great harm often has resulted when restrictions have been extended long past the time actually indicated. Thus, parents must be cautioned that such admonitions as "remember your heart," and "do not do this or that," may lay the ground work for the development of unnecessary chronic invalidism. The psychologic approach to this problem is very important for the parents and for the child, and the physician must make specific recommendations for physical activity with reassurance to the parents that the exertion allowed will not be harmful.

Management of Quiescent Phase

The rest of our time, we will devote to a consideration of preventing recurrences. This is the key feature or the motive of the quiescent phase. We will dismiss the questions of climate, diet, biologic methods of prevention, use of salicylates and confine our remarks to the use of sulphonamides in the prevention of rheumatic recrudescence. We by no means wish to be presumptuous, but for almost a decade now, sulfa compounds have been used to prevent recurrences. In most incidents, the results were considered very gratifying. The last time I reviewed some of the literature on the subject, the chances of a child who was receiving sulfa compounds continuously, of developing a flare-up of rheumatic infection, was one-tenth that of without. Even more striking however, is that major recrudescences are indeed unusual when patients are on continuous sulfa. We will take a moment to outline specific recommendations.

(1) Patient should have no evidence of activity of the rheumatic infection.

(2) Type of sulfonamide compound—most of the studies of sulfa compounds in the prevention of rheumatic recrudescences have been with sulfanilamide; and, on the whole, this has been found to be satisfactory. Various workers, however, in view of subsequent developments believe that sulfadiazine and sulfamerazine should be fully as or probably more satisfactory because of the smaller dosage required and the lesser toxic effects.

(3) Dosage—early in these investigations, 2 to 3 gm. of sulfanilamide were given in divided doses daily. Most workers now agree that small quantities are more desirable, since the maintenance of blood levels between 2 and 3 mg. appears adequate for prophylactic purposes. To produce these blood levels, sulfanilamide 0.6 gm. with the morning and evening meals is advised for the older children or adults, while 0.3 gm. three times daily is sufficient for smaller children. If sulfadiazine or sulfamerazine are used, either 1.0 gm. once daily, or 0.5 gm. twice daily is given to older children, with 0.5 gm. once daily for the younger subjects. In initiating therapy, one-half of the maintenance dose is suggested for the first week of administrations.

(4) Precautions—it is necessary to watch for signs of toxicity or idosyncrasy such as skin rashes, gastrointestinal upsets, hematuria, depression of hemoglobin, leucopenia, and agranulocytosis; fortunately these are seldom severe enough to require cessation of the drug.

(5) Blood level of sulfonamides—it is desirable to determine this early in the course of therapy and at regular intervals subsequently to determine the adequacy of the dosage. This procedure also may serve as a check on the cooperation of the patient in taking the drug.

(6) Evaluation of patient—routine examination of patients every four to six weeks is necessary in order that the physician may be constantly aware of his status and may detect any evidences of activity of the rheumatic infection.

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

EDWARDS A. PARK, *Editor*

INTRODUCTION

THE program for medical care in the State of Maryland was described as then projected by Dr. Roberts* in the *Journal of Pediatrics,* (27:384, 1945). The present article by Dr. Roberts is of especial importance because it is not only a description of the Plan in full operation but is also a progress report. Dr. Roberts has been made conscious by actual experience of the inadequacies and difficulties of the Plan as well as with its benefits and possibilities.

To my way of thinking the Maryland Plan and the North Carolina Plan, described by Dr. Arthur London in the January issue of PEDIATRICS, represent notable advances in the history of medical care in this country. They both demonstrate that, when the task of development of a medical care program is placed in the hands of representatives of the lay public and of the professions allied to medicine as well as of medicine itself the result is bound to be a broad, highly intelligent program which from the very nature of its authorship integrates into a close working union the various agencies and agents concerned with health of the community and at the same time is properly weighted in the interests of the physician and of the public.

Both the Maryland and North Carolina plans are designed to meet the need of the indigent and of the medically indigent. Is not this approach to a medical care program the best way to begin; namely, to select the group in the community which stands most in need of medical care and to attempt to plan so that that need is fully met? The kind of medical care which is provided for the lowest income groups ought not to be just general practitioner service but the most complete service which specialization and group medicine this day and generation can provide. Dr. Roberts' experience already brings out the difficulty of accomplishing this in a rural community for a small minority of the population. Certainly the way in which to make a strong beginning of building up the health of the nation is to give to those struggling most in the competition for existence and those just able to maintain themselves or actually going down all the health assistance which is available anywhere. If we can establish a model medical care

* Dr. Roberts, who was certified by the American Board of Pediatrics in 1945, has been Chief of the Bureau of Medical Services with the Maryland State Department of Health since 1945. He graduated from Emory University School of Medicine in Atlanta in 1940, and from then until beginning his work in Maryland he served on the house staff and as resident in pediatrics at The Johns Hopkins Hospital.

system for the indigent and medically indigent—and that group offers a wonderful opportunity for development by actual experiment—the medical care system will inevitably spread upwards into the lower and middle economic groups exactly to the extent to which it is useful. No artificial stimulation will be needed or desired to cause an extension upwards because the extension will be exactly in proportion to the merits, *i.e.*, the actual value of the system. Physicians should see the advantages to the medical profession as a whole, when a large segment of the population which now does not pay its medical bills becomes solvent, and it does not much matter what the source of the solvency is. So it is interesting to read in Dr. Roberts' report that already 87% of the physicians of the counties of Maryland have cooperated in the program. This does not mean that 13% have refused to cooperate but only that they have not happened to share in the work to the moment of writing.

Dr. Roberts has already discovered an unpleasant feature of the Maryland Plan in the means test. As he remarks, the means test is "basically repugnant to Americans." It is also a time-consuming, irritating, uneconomical procedure for all concerned. However, it seems to be a necessary evil in the development of a medical care plan applied only to a particular economic group. Another difficulty inherent in the Maryland Plan which Dr. Roberts has not mentioned is the fee-for-service system of payment. How can a physician be prevented from making unnecessary calls or from conniving with the patient to create a specious bill for the State to pay? The method by which this possibility is prevented at the present time is for the county board of health to submit any charge for medical services under suspicion to the county committee for investigation if need be and adjudication. At present in this time of prosperity each county physician is as busy as he can be with his private practice. But what will happen if a depression comes and the indigent and semi-indigent groups become greatly increased and the income from private practice falls off? Most physicians are honest but, as we all know, there are some who are not. The fee-for-service system of payment, however, has worked excellently in Sweden and Norway. When I asked a Norwegian physician what prevented a physician from making unnecessary calls or actually conspiring with the patient to defraud the government, he replied, "He would not dare to. What a physician does is too well known."

Both the North Carolina and the Maryland State Plans must be thought of as beginning experiments in medical care but both seem to be unusually wise and well thought out and both are being regarded by their authors as experiments and are purposely being kept fluid so that they can be changed as experience indicates. It is safe to prophesy that within the next 20 years they will be different from now and much more comprehensive and answering much better the health requirements of the people, but it seems that the general principles on which they are now founded are secure.

EDWARDS A. PARK

MEDICAL CARE IN MARYLAND

By DEAN ROBERTS, M.D., *Chief, Bureau of Medical Services*
Maryland State Department of Health

IN MARYLAND the need for comprehensive planning for health and medical care has been recognized as a problem of first magnitude. The initiative in this field was taken in 1939 by the Medical and Chirurgical Faculty of Maryland (State Medical Society) which proposed in an open letter that "a new Section or Standing Committee of the State Planning Commission be constituted, whose function it shall be to keep under constant survey the problems of medical care for the citizens of this State and to formulate from time to time recommendations for better utilization and for extension of existing medical facilities, and for the institution of such new facilities as are required." This committee is composed primarily of outstanding physicians, but includes representatives of allied professional groups as well as representatives of the public. It was organized early in 1940 and in spite of interruptions caused by the war has been extremely active. Because of the outstanding leaders who have given so generously of their talents, the committee recommendations have been supported by professional and lay groups and with few exceptions have been incorporated into law.

Maryland is a relatively small State with a population of approximately two million. About half of the population lives in the city of Baltimore, and the other half lives in the 23 counties. The counties are predominantly rural but include an urban area surrounding Washington, D.C., and a few fairly large communities such as, Cumberland, Hagerstown, Frederick and Salisbury. The medical care needs of the city of Baltimore are so different from those of the counties that they have been dealt with separately both in the studies which have been made and the programs which have been developed.

The studies of the Committee on Medical Care have covered a broad field, the most important of which are summarized below:

MEDICAL CARE IN THE COUNTIES OF MARYLAND[1]

The first project of the committee was to study the needs for medical care in the more rural parts of the State, that is, in the counties. The program which was developed is discussed in the latter part of this paper.

CONSTRUCTION OF CHRONIC HOSPITALS

The committee recognized the need for hospital facilities to care for persons suffering from chronic illness. It, therefore, endorsed the recommendations of the Almshouse Commission[2] for the construction of chronic disease hospitals. These recommendations were subsequently translated into legislation authorizing the construction of three chronic disease hospitals with a total of 1300 beds. One hospital is now in operation and a second is under construction.

LICENSING OF HOSPITALS AND NURSING HOMES

The committee's recommendation that all hospitals and nursing homes be inspected and licensed by the State Department of Health was enacted into law in 1945.

Medical Care in Baltimore City

In 1944 a special subcommittee was appointed to develop plans for medical care for low income groups in Baltimore City. A report of this committee was published in January 1947,[3] and legislation implementing the proposed program was passed later that year. This program will be described in April issue of this journal; it will be in operation early in 1948.

Survey of Hospital Facilities

Another subcommittee of the Committee on Medical Care made a detailed survey of the hospital facilities and needs of the State in accordance with the provisions of the Federal Hospital Construction Act. In accordance with the recommendations[4] of this committee the State Department of Health was named to administer the Hospital Construction Program. The committee developed a master plan for hospital construction for the State, based on a careful analysis of needs and developed a priority schedule placing most important construction first.

Tuberculosis Hospitals

The committee recommended that the administration of the four State Tuberculosis Hospitals be transferred to the State Departments of Health in order that the activities of these institutions might be more closely integrated with the program for the prevention of tuberculosis. This recommendation was implemented by a law passed in 1947.

Mental Hygiene

In dealing with the problem of mental disease, the committee made several recommendations, all of which have been subsequently adopted by appropriate bodies. It recommended that a hospital for acute psychiatric disorders be constructed as a part of the University of Maryland Hospital. It recommended that budget allocations for the administration of State mental hospitals be substantially increased to make it possible to raise standards of care. It recommended the creation of a Division of Mental Hygiene in the State Department of Health, with the responsibility of developing a non-institutional mental hygiene service utilizing the clinic facilities of the Health Department and integrated with the professional program of the State mental hospitals.

Only the first of the recommendations given above will be discussed here, but the others are mentioned in order to give emphasis to the broad planning program which has been developed and the remarkable success which the Committee on Medical Care of the State Planning Commission has had in gaining acceptance of its proposals. The Medical Care Program for the counties of Maryland is merely one segment of a much larger and broader program designed to improve the health and medical care facilities for the people of Maryland.

MEDICAL CARE FOR THE INDIGENT AND MEDICALLY INDIGENT OF THE COUNTIES OF MARYLAND

The first project of the Committee on Medical Care of the State Planning Commission was to study the needs in the counties of Maryland. A field survey of each county was carried out in order to evaluate the particular needs of individual counties. On completion of the study in 1944[1] the Planning Commission had reached the conclusion that there was no agency in the State, either official or nonofficial, whose particular responsi-

bility it was to see to it that the poor received adequate medical care. The remedial recommendations of the commission were endorsed by the State Medical Society, and in 1945 a law was passed charging the State Department of Health with the responsibility of administering a program providing medical, hospital, nursing, and dental care for the indigent and medically indigent of the State. The term "indigent" has been defined for the purposes of this program as meaning those persons who are recipients of public assistance from the Department of Public Welfare. A person is "medically indigent" when he is unable through his own resources to provide himself and his dependents with proper medical, dental, nursing, and hospital care without depriving himself or his dependents of necessary food, shelter, clothing, and similar necessities of life. The program has been in operation for two a half years and it is now possible to examine some of its strengths and weaknesses.

Development of Administrative Policies

In developing the administration of the program, the Health Department has been conscious of three basic responsibilities which must be carried out simultaneously.

1. *Responsibility to the patient:* The program resulted from public recognition of the fact that there is within the State, a group of citizens who cannot provide themselves with adequate medical care through their own resources. The program must provide this care if it is to justify its existence.

2. *Responsibility to the public:* The program is financed through general taxation. The public has a right to expect that services be provided efficiently and at reasonable cost.

3. *Responsibility to those who provide services:* Administrative policies must be kept within the area of agreement that is developed with the professional groups who provide services. Success of the program depends to a large degree on the active support and participation of physicians, dentists, nurses, pharmacies, and hospitals.

The law provides for a Council on Medical Care whose function it is to counsel with and advise the Health Department in the development of the program. This Council is a corner stone of the program. It is composed of 14 men and women, representative of the organized medical, hospital, pharmaceutical, dental and nursing professions, the State Board of Health, the State Department of Public Welfare, the Commission on Mental Hygiene, the Tuberculosis Sanatoria, and the two medical schools. The Council has met 24 times in the two and one-half years it has been in existence. Through the device of subcommittees, it has subjected every important phase of the program to intensive study and analysis. The Council, as well as the Department of Health has adopted an experimental approach toward the program. All policies are regarded as tentative and are modified from time to time in the light of experience. Although the Council is purely advisory and has no actual authority, its various recommendations have been so well thought through that with rare exceptions they have been accepted without modification by the State Board of Health.

Decentralization

Early in the development of the program it was recognized that, to be most effective, the administration of the program should be decentralized and local administrative authority placed in the hands of the County Health Departments. This plan was made

possible by the fact that since 1936 there has been a full time Health Department in each county in Maryland. The director of the County Health Department is on a full time basis and serves both as County Health Officer, and as Deputy State Health Officer. These Health Officers are all physicians and are intimately acquainted with the health and medical needs of their county. Their close association with physicians, dentists, and pharmacists has been an important factor in smoothing out administrative problems which developed from time to time.

To strengthen the Health Officer in administration of the program, a County Advisory Committee on Medical Care was organized in each county. These committees are composed of representatives of local medical, dental, and pharmaceutical societies, representatives of county departments of education, welfare and health, representatives of the County Commissioners and outstanding laymen who have demonstrated an interest in the medical care needs of low income groups. These committees meet periodically to review the progress of the program, to consider ways and means of extending and improving the services offered, and to deal with any abuses which are called to their attention. They also hear appeals of recipients of services, or persons rendering services who feel that they have a complaint to make concerning some administrative decision. The principle of local administration has been of great importance in adapting the program to varying local needs and in securing the active participation and support of professional and lay groups in the counties.

Eligibility

All persons receiving public assistance are eligible for medical care. About 15,000 such individuals are certified periodically to the Health Department by the Welfare Board. This group is referred to as the "indigent" and they are automatically supplied with identification cards establishing their eligibilty for a six-month period. If they continue on public assistance the card is renewed.

Persons who are not on relief but who are unable to pay for needed medical care have the right to make application to the County Health Department. They complete a one-page application which includes a brief statement of their financial resources. If the income is within the limitations established by the program, then they too are supplied with cards certifying their eligibility for a specific period of time. In determining eligibility, the Health Officer has broad discretionary authority to take the varying social, medical, and economic factors into consideration.

Those who are eligible are instructed, in the event of illness, to go directly to their private physician who provides those services which are indicated by the medical condition. Similarly, if dental care is needed, the patient goes directly to a private dentist. The majority of medical and dental services require no further authorization than the identification card. A few highly expensive services, such as elective surgery and dentures, require specific prior authorization.

Scope of Services

Counties are given substantial leeway in adapting the scope of service to the most pressing medical care needs in their communities. There is variation in the services offered from county to county. However, home and office care by physicians, prescribed drugs and acute dental care are provided in all counties. The majority of the counties also provide payment for hospital calls, acute and elective surgery, maternity

care, consultations, and diagnostic laboratory services. Fifteen of the twenty-three counties provide elective dental care including dentures. In many instances the limitations which counties have placed on their program have been based on the fact that certain services were already available through other community resources. For example, one county has been operating a demonstration maternity program for several years. To avoid duplication this county does not include maternity care in its program. Full use is made of the existing clinical programs of the Health Department such as the child hygiene, venereal disease, tuberculosis, and prenatal clinics. In several counties there are fairly large general hospitals with organized staffs. In these the surgeons usually rotate on service during the year and each performs surgery for indigent patients for a short period. In several such instances the physicians indicated that they desired no change in this arrangement and therefore payment for surgery is excluded from the program in those counties. Due to insufficient funds the provision of eye glasses and artificial appliances are excluded from the program. In most instances these can be provided through other community facilities. Hospitalization of the indigent is financed on a generous basis through another State fund and therefore is not included in this program.

Although the law authorized provision of bedside nursing care, the shortage of nurses as well as funds has prevented development of this service on any substantial scale. However, it was possible to obtain twenty-three additional public health nurses to supplement the existing staff and to enable them to offer more bedside nursing care on a visit basis.

The staffs of the 11 branch laboratories of the State Department of Health have been enlarged in order that they may perform clinical laboratory tests for medical care patients. Most of these laboratories are now able to offer to the physician the usual hematologic examinations, blood chemistry, urinalysis, serologic tests and bacteriologic examinations.

The Physician

The State and County Medical Societies have supported the Medical Care Program from the beginning. They are represented on the planning group, the Committee on Medical Care of the State Planning Commission. They are represented on the Council on Medical Care which guides the Board of Health in the development of administrative policies, and they are represented on each County Advisory Committee.

At the end of each month the physician submits a simplified medical report for each patient whom he has treated during the month under the program. This report is reviewed and approved by the County Health Officer and forwarded to the State Office, from which payment is issued. There are approximately 20,000 persons in the counties who are in possession of certificates of eligibility. Of this number between 3,000 and 4,000 receive physicians' services each month. Up to the present time 807 physicians have participated in the program. A substantial number of these physicians have their offices in Baltimore City (not in any county) and a few are out of State. The majority of the physicians, however, have their offices in one of the counties. There are 693 physicians in the counties, and of these 592 or 87% have participated in the program. The number of physicians participating each month is approximately 430. It will be seen that the majority of physicians are taking an active part in the program. This is also true of dentists and pharmacists. There is no limitation on the amount or type of service a physician renders or on the drugs he prescribes. Payment is on the fee-for-

service principle following a uniform fee schedule recommended by the Council on Medical Care.

Costs: The program is operating with an annual appropriation of $460,000. Since the population of the counties is about one million, this amounts to a per capita expense of 46 cents per year. Monthly expenditures are currently at the rate of $36,465. Over a recent nine month period the breakdown of expenditures was as follows: 78% for physician care; 7% for dental services; 15% for drugs; 1% miscellaneous other services.

There are approximately 15,000 recipients of public assistance in the counties, and this constitutes the eligible "indigent" population. Each month about 15% of these receive physician services. The cost of providing care to this group is approximately $16.00 per person per year.

Due to the limited appropriation only a small number of medically indigent persons have been certified to the program. This group accounts for about 24% of the patients receiving care from physicians and 35.2% of the patients receiving dental services. The cost per case for this group is substantially higher than for the indigent, primarily because the medically indigent tend to be certified only in the event of serious illness, whereas the indigent are automatically certified whether they are sick or not. They receive care of minor as well as serious illnesses.

Limitations of the Program

There are a number of factors which place limitations on this program. The law defines the program as being for the indigent and medically indigent. It is, therefore, necessary to apply a means test to determine eligibility. Application of a means test is expensive and technically difficult. No matter how carefully the test is devised and regardless of how skillfully it is applied at the local level, there will always be those who complain that the test is too liberal and others that it is too strict. In addition, the matter of subjecting citizens to a means test is basically repugnant to Americans and unless skillfully administered tends to lower the individual's self-respect. This problem is not one which can be overcome within the present framework.

As described previously the services are purchased on the fee-for-service principle. Medical care purchased in this manner tends to be expensive and is subject to abuse unless safeguards are established. The constant review of experience of the program by County Advisory Committes has been very valuable in reducing abuses to a minimum. The fee-for-service system is not conducive to full emphasis on preventive medicine as contrasted to curative medicine. The preventive services must be offered largely through Health Department clinics.

In a program of this type it is rather difficult to have any substantial influence on the quality of service rendered. The program is purchasing for the low income group the same type and quality of care as is generally available to the community. There are large areas in Maryland which lack adequate diagnostic and consultation services. It is uneconomical, however, to establish new facilities through a program which is serving only 2% of the population.

Possibilities of the Program

In spite of the limitations described above, the program offers many opportunities for experimentation in ways of improving and extending health services. Several small

scale projects are underway in particular counties, which may later lead to significant improvements in the program. In one county a demonstration is in progress which within a year or two may answer some of the questions regarding the amount and type of nursing service needed in rural communities. In this county the number of public health nurses has been increased to a ratio of one nurse to each 2,800 population. In addition to the usual public health services, the nurses are offering bedside nursing care on a visit basis for all patients referred by physicians. Under the direction of the private physician the nurse will go into the home as often as needed, give the usual bedside care, administer prescribed medications and carry out any other nursing orders left by the physician. It is hoped that with this service it will be possible for some patients who formerly would have been hospitalized to receive adequate care in the home. This service may also make it possible for physicians to reduce the number of home calls.

In another county it was possible to have two-thirds of the patients under the program examined by a dentist and the dental defects charted. On the basis of this survey and others which will be carried out later, the dental phase of the program will be modified so as more nearly to meet the actual dental needs of patients.

The extension of services offered by branch laboratories to include clinical laboratory procedures will enable physicians to make more accurate diagnoses and thereby improve the quality of care. Many of these laboratories are in areas of the State where no other clinical laboratory facilities are available. One objective of the program is the establishment of clinics for the periodic examination of well adults. Such clinics would be conducted along the lines of well baby clinics, and cancer detection clinics which have already demonstrated their usefulness. The examinations performed in these clinics would be adapted to the conditions most likely to occur in particular age and sex groups. The development of a series of consultation clinics in the major specialties is envisioned for the more rural areas of the State. Some such clinics have previously been established in pediatrics, obstetrics, orthopedics, otology, and cardiology. Most of these were in existence prior to the development of the Medical Care Program. It is proposed that they be extended to cover the other major specialty fields in the counties which need them and in which the physicians express a desire to have them. As pointed out previously, one of the difficulties in establishing clinics of this type is the fact that the Medical Care Program provides service to only a small fraction of the population. If consultation clinics are developed on any wide scale it will probably be necessary to work out a plan whereby they may be utilized by a larger segment of the population.

One of the most significant achievements of the program has been the development of County Advisory Committees on Medical Care. In several counties these committees have developed into highly significant community groups which concern themselves with all aspects of the health needs of the community whether related to the Medical Care Program or not. They have served to bring together community agencies which previously had functioned without relationship to each other. The future development and expansion of these committees can prove to be a valuable tool in a continuing analysis of the health and medical care needs of the community, and in developing new resources designed to meet these needs.

Summary

Maryland has developed a highly effective instrument for analyzing and developing plans to meet health and medical needs through the standing Committee on Medical

Care of the State Planning Commission. One of the recommendations of this committee has resulted in development of a Medical Care Program for low income groups in the counties. Administration of this program has been worked out jointly by the Health Department, which is the administrative agency, and the professional groups which are called upon to provide the services. The program assures persons in low income groups of access to a type and quantity of medical care which is about on a par with the care which is generally available in the community for patients who can afford to pay. Physicians are assured of reasonable payment for their services to this group, and are thus relieved of a heavy burden of charity practice. Through development of new diagnostic laboratory facilities in branch laboratories of the Health Department, development of consultation clinics, and through extension of bedside nursing care, the program promises to have a favorable influence on the quality of care provided. The program offers numerous other opportunities for experimentation in methods of improving the quality of medical care.

The endorsement of the program by the medical profession represents an important landmark in Maryland. It represents the finding of a common ground of agreement as regards medical care between the State government and the medical profession. The responsibility of government to provide care for the medically indigent is clearly recognized, and a framework is established for a developing partnership between government and the profession, with the goal of bringing high quality care to a group of the population who in the past have received grossly inadequate medical care. The importance of this common ground of agreement between government and the medical profession cannot be overemphasized.

The discussion of public medical care has frequently been so inflamed by proposals totally unacceptable to professional groups that many have gained the impression that cooperation toward a common goal is impossible. Professional groups resist sweeping proposals placing government in a dominant position in medicine because they are afraid of what it will do to them as individuals and as professional groups. This seeming impasse can be resolved if agreement can be achieved on limited programs and if government can administer these limited programs in such a way as to provide improved services through administrative methods acceptable to physicians, dentists, and hospitals. Mutual confidence of professional groups and government will be gained, not by angry debate, but by cooperative exploration of areas of agreement.

December 1, 1947

References

1. Medical Care in the Counties of Maryland, Report of the Committee on Medical Care of the Maryland State Planning Commission, April, 1944.
2. Report of the Almshouse Commission, Submitted to the governor of Maryland, November 22, 1940.
3. Interim Report of Committee on Medical Care, Maryland State Planning Commission, January, 1947.
4. Hospital Survey and Plan for the State of Maryland, Hospital Survey Committee of the Maryland State Planning Commission, June, 1947.

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer, nor are they to be interpreted as official opinion of the Academy.

FEDERAL FUNDS FOR TEACHING

A MONTH ago attention was called to the fact that the U. S. Public Health Service and the U. S. Children's Bureau have been urged to study the problem of medical education and make plans to subsidize medical schools. This recommendation fell on fertile soil, and may be expected to bear fruit in the near future. It is timely, therefore, to review the extent to which medical education is already supported financially by the federal government.

The National Cancer Institute, a branch of the National Institute of Health of the U. S. Public Health Service, has been allowed a total appropriation of $14,000,000 for the fiscal year ending June 30, 1948. In addition to providing for cancer research, the act which establishes the Institute (Public Law 244 of the 75th Congress) authorizes the Surgeon General "to provide training and instruction in technical matters relating to the diagnosis and treatment of cancer; to provide fellowships in the Institute from funds appropriated or donated for such purpose." In accordance with this authorization, $1,500,000 has been allocated for the current fiscal year for "medical school education grants." Grants not to exceed $25,000 are allowed for four-year medical schools for teaching related to cancer; grants not to exceed $5,000 for the two-year schools; and grants not to exceed $5,000 for dental schools. As of February 1, 1948, a total of $894,728 has been made to 40 medical schools; grants of $58,209 have been made to 12 schools of dentistry. These funds provide for teaching salaries and equipment for teaching (about half of an individual grant is usually budgeted for equipment and teaching aid). In addition to these grants, which are related primarily to undergraduate teaching, a fund of $250,000 has been established for clinical trainee-ships, for the purpose of assisting young physicians with special interest in cancer problems to continue their training long enough to acquire special knowledge. Seventy-five trainee-ships have been granted on a per diem basis at a rate not to exceed $10 a day.

It is the hope of the Cancer Institute that the assistance for which provision is now made will effect better integration of the many individual courses now given on cancer in medical and dental schools.

The National Mental Health Program, in addition to its other activities, provides for "training personnel in matters relating to mental health." Under provisions of Public Law 487 of the 79th Congress, the Surgeon General is authorized "to provide training and instruction in matters relating to psychiatric disorders . . . and to provide such training and instruction, and demonstrations, through grants, upon recommendation of the National Advisory Mental Health Council, to public and other non-profit institutions." For the current fiscal year ending June 30, 1948, an appropriation of $7,500,000 was authorized for the National Mental Health Program and other activities. Of the total appropriation, over $1,000,000 has been allocated for grants to institutions for the de-

velopment and improvement of facilities for training mental health personnel. Grants have been awarded to universities, hospitals, and clinics at undergraduate, graduate, and postgraduate levels, for training in the fields of psychiatry, clinical psychology, psychiatric social work, and psychiatric nursing. Provision is also made for scholarships and fellowships in psychiatry, psychology and related subjects.

In addition to the grants made directly to teaching institutions, a sum of $3,000,000 has been allocated for grants-in-aid to states for local mental health programs. A considerable proportion of these grants also are available for fellowships for graduate or postgraduate students.

An increase in the appropriation for the National Mental Health Program has been recommended by President Truman for the fiscal year ending June 30, 1949. In his budget message to Congress the President recommended an appropriation of $10,416,000, an increase of almost $3,000,000, to provide additional grants for training of mental health personnel.

The U. S. Children's Bureau is a third source of federal funds for medical education. Dr. Edwin F. Daily, Director of the Division of Health Services, describes* this aspect of the Bureau's activities as follows:

"The Social Security Act of 1935 authorizes the Children's Bureau to make grants-in-aid to State agencies for extending and improving maternal and child health and crippled children's services. Many of the State agencies have used portions of these grants for the training of personnel needed to render the services. All such grants must, by law, be made to the official State agency and cannot be made directly from the Children's Bureau to teaching institutions, as allowed under the national cancer program or the national mental health program. State health agencies have used these funds under agreements with several medical schools, including the Universities of Nebraska, Colorado, Utah, Louisiana, Arkansas, and Meharry Medical College, to further education and service programs. These projects are not confined entirely to teaching purposes but cover service costs as well, as for example, in the Premature Program at the University of Colorado or the Louisiana State University. Several Schools of Public Health, of Dentistry, Nursing, and Medical Social Work have also received Federal Maternal and Child Health funds from their State health departments for developing postgraduate courses needed for the personnel providing services under these programs. During the current year more than $1,000,000 of the $18,500,000 of Federal funds available for maternal and child health and crippled children's services is being expended by the States for the training of personnel and in connection with educational institutions."

A fourth source of federal funds for medical education, and one which is not widely known, is in support of Howard University. In 1867, Howard University was established as a federal institution for Negro education. The University was transferred from the Department of Interior to the Federal Security Agency in 1940. At the present time, the federal government's share in the budget of the University as a whole is 51%. Seventy-eight per cent of the present budget of the College of Medicine is provided by the federal government, with the remainder being met by private endowments.

The National Heart Disease Program

Two bills, which are almost identical, have been introduced into the House to provide for a National Heart Disease Program. In the midst of Republican and Democratic

* Personal communication to the author.

squabbling, it is gratifying to see an element of harmony in the sponsorship of a heart program. Representative Keefe (Republican) introduced H.R. 5087 on January 21, 1948, and Representative Smathers (Democrat) introduced H.R. 5159. Both bills propose to provide for research, prevention, diagnosis and treatment related to diseases of the heart and circulation, including hypertension.

The bills propose grants-in-aid to universities, hospitals, laboratories, other agencies, and individuals and for "training research workers; training undergraduate and post-graduate personnel in matters relating to heart diseases; and developing and assisting States and other agencies in the use of the most effective methods of prevention, diagnosis and treatment of heart diseases, including refresher courses for physicians . . ." (The latter clause is included in H.R. 5159 but not in H.R. 5087). If this legislation should be enacted, an additional source of financial support of medical education would be established.

It is proposed to create a National Heart Council, appointed by the Surgeon General. This Council would serve in an advisory capacity in much the same manner as is now done by the National Advisory Cancer Council and the National Advisory Mental Health Council.

In order to finance the program, the bills authorize an appropriation for "such sums as the Congress may determine to be necessary to carry out the provisions of this act." The amount is not stated but is left entirely open for further Congressional action. Worthy of note in this connection is the fact that Congressman Keefe is Chairman of the House Appropriations Subcommittee which handles annual funds bills for the Federal Security Agency.

An item of special interest is the fact that the bills authorize salaries ranging from $10,000 to $15,000 "for the services of specially qualified scientific and professional personnel"—a hopeful portent of salaries adequate to attract to government positions professional and scientific personnel of high caliber.

* * *

Hearings on the Taft (S. 545) and Murray-Wagner-Dingell (S. 1320) bills for a national health program were resumed on January 26, 1948 before the Senate Labor and Public Welfare Subcommittee on Health. Chief witness of the opening session was Mr. Isadore Falk, Director of the Bureau of Research and Statistics, Social Security Administration, who was questioned at length as to the part played by the Federal Security Agency in the preparation of S. 1320. Others who have been heard include Dr. Marjorie Shearon, collector of facts and opinions in support of S. 545. It is anticipated that these hearings will be concluded soon.

* * *

Another item of immediate interest is a message from President Truman to Mr. Oscar R. Ewing, Administrator of the Federal Security Agency. The President asks Mr. Ewing "to undertake a comprehensive study of the possibilities of raising health levels and to report to me at your earliest convenience upon feasible goals which might be realized by the American people in the next decade." Having been charged with this assignment, the FSA may be expected to develop a 10-year plan predicated not only upon adoption of national health insurance but also upon elevation of the FSA to cabinet status as proposed in the Taft-Fulbright-Aiken bill (S. 140).

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, *Contributing Editor*

NATIONAL CONFERENCE ON FAMILY LIFE, WASHINGTON, D.C., MAY 6, 7, AND 8, 1948

THE idea of holding a National Conference on Family Life was developed in 1944 by the American Home Economics Association, which enlisted the interest of the National Planning Association in developing such a conference. By June 1946 more than a hundred national organizations had sponsored the undertaking and the president had offered the courtesy of the White House "as a place of meeting and as evidence of my official and personal interest." To date the sponsoring organizations are composed of 125 national organizations, with a total membership of forty million peoples. Included in these sponsoring organizations are: the American Medical Association, the American Dental Association, and the American Academy of Pediatrics.

The conference proposes to consider the problems that are facing the American family today. Their announcement points out that:

"For generations, the church, the school and social and other agencies have been aware of an increasing number of problems which tend to cripple and destroy family life. Through study and application of experience, they have worked out many satisfactory methods of meeting these problems.

"In recent years there has been a mounting interest on the part of numerous sciences, organizations and governmental departments in special aspects of family life. Each has developed a fund of information, experience and practical knowledge which, taken altogether, could be a substantial safeguard for every family in America.

"The problem is so complicated, however, that up to this time there has been little or no success in treating the family as a unit. When the doctor is called in, he has a patient—mother, father or child—and he orders hospitalization, or segregation, or treatment without regard to what his recommendations mean to the family as a whole. The school teacher instructs the child without understanding what results the instruction may have on the family. Youth agencies provide activities for young people which may increase their appreciation of family life but equally may alienate them from their parents, brothers and sisters.

"The fact is that while we consider the family the essence and core of American life, the problems and needs of individual members of the family have become so complex that our sciences, agencies and organizations are attempting to meet these problems without regard—or with only lip service—to the family as a whole. . . .

"There is no simple solution for the wide variety of problems which American families must face today. What has been learned about solving them through the experience and study of the many sciences and organizations working in this field must be pooled into one body of knowledge. It will then be possible for them to create more effective policies and programs which will provide a sound foundation for action by

Data furnished by the Division of Public Health Methods, United States Public Health Service.

everyone. It is for this purpose that the National Conference on Family Life was called."

This will be the first conference of its kind ever undertaken. Primarily, it will be composed of working groups in which representatives of at least 125 national organizations will take part. Though there will be several large general sessions, it is from these working groups that the findings of the Conference will come.

FEDERAL SECURITY AGENCY REPORTS PUBLIC HEALTH VACANCIES

UNFILLED professional vacancies in State and local health departments of 12 States, totaling 590 more than in 1945, were disclosed recently when the Committee on Training of Public Health Personnel, U. S. Public Health Service, Federal Security Agency, announced the results of a spot survey made last spring.

The Committee conducted the survey in April 1947 as a follow-up of a compilation made in July 1945. At that time, 38 State and 930 local health departments reported a total of 2,593 vacancies in 19 categories of full-time positions, and 2,000 positions being held for persons in the armed services.

Although incomplete information was supplied by 8 of the 12 States queried last spring, a total of 1,847 unfilled jobs were reported in the same 19 categories for which the 12 States recorded 1,257 vacancies in July 1945. Replies from these States indicated that the impact of medical men returning from military duty had not yet been felt.

In 13 of the 19 types of positions, vacancies reported in 1947 were greater than in July 1945. Prominent totals among unfilled positions in the 12 States spot-checked last April were: Health officers, 117 (55 in 1945); medical officers, 186 (101 in 1945); graduate nurses, 940 (654 in 1945); sanitary and public health engineers, 81 (36 in 1945).

Results of the sampling were printed in full in the November 21, 1947, issue of Public Health Reports, weekly scientific publication of the Public Health Service. States included in the spot survey were: California, Colorado, Georgia, Illinois, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, New York (exclusive of New York City), North Carolina and Texas.

INCIDENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES, JANUARY 4-31, 1948*

The accompanying table summarizes the incidence of nine important communicable diseases, based on weekly telegraphic reports from State health departments. The reports from each State for each week are published in PUBLIC HEALTH REPORTS under the section "Incidence of Disease."

Diseases Above Median Incidence

Influenza.—For the 4 weeks ended January 31 there were 46,735 cases of influenza reported. During the corresponding 4 weeks in 1947 there were 16,910 cases reported and the median for the

* The data contained in these reports are based upon thirteen 4-week periods with the first week in each year ending between the 4th and the 10th of January. This of necessity makes an extra week in an occasional year over a period of years, as was the case in 1947. The first week of the current 4-week period ended January 10, that being the first 7-day week in 1948.

preceding 5 years (1943-47) was 17,421 cases. The incidence has been largely confined to the South Atlantic, South Central, and Far Western sections. Of the total cases, Texas reported 19,336, California 5,220, Arizona 4,828, South Carolina 4,293, Virginia 3,635, Alabama 2,462, and Arkansas 2,076 cases. Almost 90 percent of the total cases were reported from those 7 States. Minor increases in other States in the South Central sections also contributed to the relatively high incidence in those sections; in the East South Central section the number of cases (3,252) was 2.6 times the median and in the West South Central section the number of cases (22,851) was 2.3 times the seasonal median expectancy. Few cases are being reported from the North Atlantic and North Central sections.

Measles.—There were 33,211 cases of measles reported for the current 4-week period as compared with 15,020 for the corresponding 4 weeks in 1947 and a 1943-47 median of 20,285 cases. Significant increases over the seasonal expectancy were reported from the Middle Atlantic, North Central, South Atlantic, West South Central, and Pacific sections while in the New England, East South Central, and Mountain sections the incidence was considerably below normal. For the country as a whole the current incidence was the highest since 1944 when approximately 50,000 cases were reported for the corresponding weeks.

Poliomyelitis.—While the number of cases (160) of poliomyelitis was only about 50 percent of the number reported for the corresponding period in 1947 it was 8 percent above the median for the preceding 5 years (1943-47). Of the total number of cases, New York reported 18, Washington 16, Idaho 14, California 13, Oregon 12, and North Carolina 11; more than one-half of the cases were reported from those 6 States. The South Atlantic and Mountain sections reported rather significant increases over the 1943-47 medians; in the Middle Atlantic and Pacific sections the increases were very slight, and all other sections reported a decrease from the normal seasonal median.

Whooping cough.—The number of cases of whooping cough (9,440) compared very favorably with the incidence for the corresponding weeks in 1947 and was only 1.1 times the 1943-47 median. The incidence was higher than the median for the preceding 5 years in the East North Central, West North Central, East South Central, and Mountain sections, and lower than the seasonal expectancy in the Atlantic Coast, East South Central, and Pacific sections.

Diseases Below Median Incidence

Diphtheria.—For the 4 weeks ended January 31 there were 979 cases of diphtheria reported. The number of cases was slightly less than 80 percent of the incidence for the corresponding period in 1947 and 72 percent of the median for the preceding 5 years (1,355 cases). For the country as a whole the current incidence was the lowest for this period since 1944 when 1,059 cases were reported for the corresponding 4 weeks. In the South Atlantic section the number of cases (267) was about 15 percent above the normal seasonal expectancy and in the Mountain section the number (85) was 35 percent above the preceding 5-year median; in all other sections the incidence was relatively low.

Meningococcus meningitis.—The number of cases (332) of meningococcus meningitis reported for the current 4-week period was only slightly below the number reported for the corresponding period in 1947, but it was less than 35 percent of the 1943-47 median. Each section of the country shared in the more favorable situation of this disease that now exists, the current incidence for the country as a whole being the lowest since 1942 when 230 cases were reported for the corresponding weeks.

Scarlet fever.—For the 4 weeks ended January 31 there were 8,457 cases of scarlet fever reported. There were 9,525 cases reported for the corresponding 4 weeks in 1947, with a 1943-47 median of 14,150 cases. Since 1944 this disease has been on the downward swing of a long-term cycle and for this particular period the incidence was the lowest on record. Decreases from the 5-year median in the various regions ranged from 30 percent in the East South Central section to about 60 percent each in the New England and Mountain sections.

Smallpox.—There were 11 cases of smallpox reported during the current 4-week period, as compared with 17 cases during the corresponding period in 1947 and a 5-year (1943-47) median of 34 cases. The number was the lowest on record for these same weeks. Two cases each were reported from Missouri and Kansas but no other State reported more than one case.

Typhoid and paratyphoid fever.—The incidence of these diseases continued at a relatively low level, the number of cases (153) reported for the 4 weeks ended January 31 being slightly below the record of last year and only about 75 percent of the median for the preceding 5 years. Slight

increases over the normal seasonal expectancy were reported from the West South Central and Pacific regions of the country, but in the other 7 sections the numbers of cases were below the seasonal medians.

Mortality, All Causes

For the 4 weeks ended January 31 there were 42,190 deaths from all causes reported to the National Office of Vital Statistics by 93 large cities. The number of deaths was higher than the 1945-47 median for each week of the current 4-week period. The median number of deaths was 40,625 which is 3.7 percent less than the total deaths for the current 4 weeks.

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD JANUARY 4–31, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	979	1,277	1,355	46,735	16,910	17,421	33,211	15,020	20,285
New England	23	95	44	14	73	147	1,324	3,834	3,336
Middle Atlantic	121	185	152	28	86	187	6,492	4,435	4,731
East North Central	105	168	168	473	223	571	12,848	2,054	3,786
West North Central	64	93	117	363	399	404	3,092	228	1,786
South Atlantic	267	229	229	8,800	5,530	6,163	2,307	2,324	1,498
East South Central	97	149	129	3,252	438	1,244	479	186	1,059
West South Central	146	180	309	22,851	8,804	9,774	3,248	425	788
Mountain	85	57	66	5,427	1,248	1,248	940	1,000	1,265
Pacific	71	121	158	5,527	109	365	2,481	534	1,881
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	332	344	953	160	315	147	8,457	9,525	14,150
New England	21	22	43	3	13	10	645	1,020	1,666
Middle Atlantic	56	61	205	28	27	27	1,902	2,228	2,732
East North Central	43	50	165	14	68	23	2,682	2,953	4,032
West North Central	22	37	79	8	37	13	788	813	1,445
South Atlantic	43	54	131	21	30	14	662	781	1,198
East South Central	31	43	91	7	18	10	414	365	581
West South Central	48	34	88	17	28	28	309	211	484
Mountain	11	11	25	21	20	13	359	445	929
Pacific	57	32	111	41	74	39	696	709	1,171
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	11	17	34	153	166	201	9,440	9,500	8,985
New England	0	0	0	9	18	7	1,101	1,127	1,127
Middle Atlantic	0	0	0	24	28	28	1,261	2,328	2,029
East North Central	1	9	7	9	19	21	1,742	2,499	1,529
West North Central	4	2	3	3	10	9	730	272	426
South Atlantic	0	1	1	32	16	38	1,283	1,098	1,302
East South Central	1	2	6	12	20	14	308	369	346
West South Central	2	2	6	40	27	36	1,738	1,136	949
Mountain	3	1	9	5	14	14	713	174	323
Pacific	0	0	2	19	14	14	564	497	743

[1] New York, North Carolina, and Pennsylvania excluded; New York City and Philadelphia included.

BOOK REVIEWS

RESEARCHES ON NORMAL AND DEFECTIVE COLOUR VISION, by W. D. Wright A.R.C.S. D.Sc. (Reader in the Imperial College of Science and Technology, London), $10.00, 383 pages, 233 illustrations. Whitefriars Press, Ltd., London, The C. V. Mosby Co., St. Louis 3, Mo., 1947.

Because Wright is considered one of the authorities today in the field of color, this book warrants the attention of all interested in color physiology. The book describes and summarizes with unusual completeness the results of most of the recent experimental research, and points out the theoretical implications of those results with the emphasis placed on the physiology involved. Although the author describes the experimental works of others, he devotes most of the book to his own research or to that of the Imperial College of Science and Technology in London. The book is written in a technical lanuage. While it will prove interesting and much of it will prove understandable to the layman, it certainly is not written for him.

In order to provide a background for the various aspects of color, Wright devotes the first few chapters to the well-known facts of visual physiology and physiologic optics. Two chapters are given to his design and the construction of a modern and versatile trichromatic colorimeter which makes use of spectral primaries. The following chapters then take up (1) the luminosity curves, under both photopic and scotopic illuminations, for the foveal and extrafoveal regions and with very restricted fields; (2) the problems and experimental results of color mixtures, the chromaticity diagram for specifying color mixtures, the determination of the trichromatic coefficients and the colorimetric curves for the normal observer; (3) the interpretation of the color mixture facts in terms of the Young-Helmholtz three-response hypothesis; (4) the experimental results on the sensitivity of the eye in discriminating differences in hue, saturation and combinations of both (Wright defends the Weber-Fechner laws by insisting on a more logical interpretation of their theoretical bases); (5) the depression of the light sensitivity of the retina and change in color discrimination due to adaptation by white and colored light, and the recovery rates to such adaptation; (6) the binocular matching of colors under various test conditions and monocular adaptation; (7) a consideration of the nature of the three fundamental color stimuli from the spectral curves of color matching; (8) subjective brightness and its method of measurement. Wright suggests as the unit of subjective brightness, the *Brill*, a unit which is proportional to the logarithm of the objective luminosity.

The remaining third of the book is devoted to defective vision, with a rather good discussion of anomalous trichromatism (only slightly below normal in some aspects of color discrimination) and dichromatism (loss of ability to discriminate hues in one portion of the spectrum—protanopia [red "blindness"] and deuteranopia [blue-green "blindness"]). The methods of testing for color deficiencies and their limitations are only briefly considered, as also are the hereditary aspects of defective color vision. A chapter is given to the "blue blindness" of the central fovea. The several types of color blindness are interpreted with respect to the chromaticity diagram and the three color hypothesis. The interpretation of the many aspects of color visual phenomena as related to the role of the fundamental response curves of color discrimination is presented in the last chapter.

Because this book is complete and up-to-date, it is recommended as a reference text and to anyone who wishes to study seriously the essential facts of color physiology.

KENNETH N. OGLE, M.D.

DISEASES OF CHILDREN'S EYES, by James Hamilton Doggart, M.A., M.D., F.R.C.S., $10.00, 288 pages, 210 illustrations, 32 colored plates. The C. V. Mosby Co., St. Louis 3, 1947.

This book should be useful to those interested in pediatric ophthalmology. The content of the book is largely the same as found in standard texts on ophthalmology. It is, however, well arranged, well illustrated, and condensed. Throughout the text the author has stressed the theme of the child as related to ophthalmology. The chapters on principles of examination, developmental and congenital

anomalies, methods of treatment, and ocular welfare are handled in a practical manner and with much common sense.

R. L. J. KENNEDY, M.D.
A. G. PRAUGEN, M.D.

PEDIATRIC PROGRESS IN THERAPEUTICS OF INFANCY AND CHILDHOOD, edited by Harry R. Litchfield, M.D., and Leon H. Dembo, M.D., $8.00, 512 pages, 106 illustrations (Including 28 Graphic Growth Grids). F. A. Davis Company, Philadelphia 3, 1948.

This volume inaugurates another periodic presentation of selected subjects by various authors in the field of pediatrics. It is related to and supplements a multiple-volume work on "Therapeutics of Infancy and Childhood" by the same principal authors. Articles have been selected which are of practical application and, therefore, are restricted in coverage of all recent advances in therapeutics.

The chapter headings and authors are as follows: "The Use of the Grid Technic as a Guide to the Treatment of Diseases Causing Growth Failure in Children" by Norman C. Wetzel, M.D.; "Dysenteries and the Salmonella Infections" by Joseph Felsen, M.D.; "Cystic Fibrosis of the Pancreas" by Paul E. A. di Saint 'Agnese, M.D.; "Thiourea Drugs in Hyperthyroidism" by Bernard Seligman, M.D.; "Coburn Treatment of Rheumatic Fever" by Walter Heymann, M.D.; "The Clinical Use of Normal Human Serum-Gamma Globulin" by William Berenberg, M.D.; "Antibiotic Therapy" by Charles Solomon, M.D.; "Viral Hepatitis" by Richard B. Capps, M.D.; "Toxoplasmosis," "Virus Pneumonia," and "Amino Acids" by Harry R. Litchfield, M.D.; "Folic Acid" by Samuel Saslaw, Ph.D., M.D.; "Advances in the Treatment of the Diseases of Allergy" by Leo H. Criep, M.D.; "Newer Knowledge of the RH Blood Types and Their Clinical Applications" by Alexander S. Wiener, M.D.; "Recent Advances in the Treatment of Malaria" by Harry Most, M.D.; "Hernia in Infants and Children" by Alfred H. Iason, M.D.; "Treatment of Convulsions" by M. G. Peterman, M.D.; "Histoplasmosis" by Royal M. Montgomery, M.D.; "Penicillin in Treatment of Congenital Syphilis" by Joseph Yampolsky, M.D.

Each article represents a review of the recent advances in that particular field. Some of them do not have bibliographies included.

AIDS TO THE DIAGNOSIS AND TREATMENT OF DISEASES OF CHILDREN, by F. M. B. Allen, M.D., F.R.C.P. (Lond.) Lecturer on Infant Hygiene and Diseases of Children, Queen's University, Belfast, $2.00. Eighth edition, 268 pages. Bailliére, Tindall and Cox, London W.C.2, The Williams & Wilkins Co., Baltimore 2, 1947.

The present edition appears six years after the seventh. It records the recent advances particularly as regards the chapter on infectious fevers. A small pocket-sized textbook without illustrations and bibliography. The text is condensed to barest essentials. It should be useful to undergraduate students and to general practitioners who require a brief descriptive reference. The information seems reliable for such purposes. A short list of prescriptions seems archaic and superfluous.

CHEMISTRY OF FOOD AND NUTRITION, by Henry C. Sherman, Ph.D., Sc.D. Seventh Edition, $4.00, 675 pages, 47 figures. The Macmillan Company, New York 11, 1947.

While this book is designed primarily for students in college classes, it should be of service to many other types of readers. Essential changes have been made in the text, several chapters have been rewritten, and two new chapters dealing with the nutritive characteristics of the chief group of foods and the causes and extent of variations in the nutritive values of food have been added. These values have been revised in accordance with the recent dietary recommendations and studies of food values by the Federal Government and the National Research Council.

NEWS AND ANNOUNCEMENTS

Helen B. Taussig, M.D., associate professor of pediatrics at Johns Hopkins University, received the Legion of Honor from the French government in Paris last fall for her work in originating a system to treat "blue babies."

Dr. Albert H. Montgomery, Associate Member, died recently at his home in Chicago, Ill.

The following doctors were certified by the American Board of Pediatrics after their examinations in Philadelphia, Pa., on January 9, 10 and 11, 1948. The total number certified is now 2749.

Kenneith M. Alford, M.D., 159 Bidwell Parkway, Buffalo, New York
Edward Bailey, M.D., 166-19 89th Avenue, Jamaica, New York
Evelyn J. Basile, M.D., 20 8th Avenue, Brooklyn, New York
Marvin L. Blumberg, M.D., 65-60 Booth Street, Forest Hills, New York
Benjamin Wells Bullen, Jr., M.D., 149 Field Point Road, Greenwich, Connecticut
John A. Burke, M.D., 337 Appleton Street, Boston, Massachusetts
Arthur Wayson Chung, M.D., 295 West 11th Street, New York City, New York
Charles Louis Dimmler, Jr., M.D., 2940 Summit Street, Oakland, California
Emanuel Fletcher, M.D., 140-10 Franklin Avenue, Flushing, New York
Alfred Leonard Florman, M.D., 35-24 78th Street, Jackson Heights, New York
John E. Gainor, M.D., 3 Groesbeck Place, Delmar, New York
I. Gershman, M.D., 343 Thayer Street, Providence, Rhode Island
Harry Gibel, M.D., 1171 Eastern Parkway, Brooklyn, New York
Arthur A. Goldfarb, M.D., 1150 Grand Concourse, New York City, New York
David McLean Greeley, M.D., Babies' Hospital, New York City, New York
Joseph A. Hesch, M.D., 5821 Beaumont, Philadelphia, Pennsylvania
Deborah B. Kaplan, M.D., Beard Building, 3 Main Street, Cortland, New York
Thomas T. Kochenderfer, M.D., 1451 DeKalb Street, Norristown, Pennsylvania
Ella Langer, M.D., 96 State Street, Augusta, Maine
Marion McIlveen, M.D., 88 West Ridgewood Avenue, Ridgewood, New Jersey
Harry S. Mackler, M.D., 752 North Broad Street, Elizabeth, New Jersey
Hyman Merenstein, M.D., 1324 48th Street, Brooklyn, New York
Julius Yoland Miller, M.D., 1874 Commonwealth Avenue, Brighton, Massachusetts
Doris H. Milman, M.D., 126 Westminster Road, Brooklyn, New York
Frederic Clifford Moll, M.D., 300 Longwood Avenue, Boston, Massachusetts
Marguerite Mary Neylan, M.D., 482 Beacon Street, Boston, Massachusetts
John Richard O'Connell, M.D., 27 Ludlow Street, Yonkers, New York
William Obrinsky, M.D., 50 West 96th Street, New York City, New York
Faith Newbury Ogden, M.D., 6 Stevens Street, Norwalk, Connecticut
Pauline Owyang, M.D., Department of Public Health, 8 Beacon St., Boston, Mass.
Archibald Hanes Pate, M.D., 403 Borden Building, Goldsboro, North Carolina
R. William Provenzano, M.D., 520 Commonwealth Avenue, Boston, Massachusetts
Josephine Perlingiero Randall, M.D., University of Pennsylvania, 3600 Spruce St., Philadelphia, Pa.
Nathan Ravin, M.D., 1185 Grant Avenue, New York City, New York
Thomas B. Re, M.D., 420 50th Street, Brooklyn, New York
Anthony Joseph Repici, M.D., 212 Haddon Avenue, Haddonfield, New Jersey
Frederick Newton Roberts, M.D., 418 East Genesee St., Syracuse, New York
J. Winfield Scott, M.D., 3209 N. Meridian Street, Indianapolis, Indiana
Charles F. Shevlin, M.D., 167-05 Hillside Avenue, Jamaica, New York
Milton Singer, M.D., 69 East 76th Street, New York City, New York
Alfred Benjamin Stein, M.D., 959 East 55th Street, Chicago, Illinois
Norbert Paul Sullivan, M.D., 35-35 82nd Street, Jackson Heights, New York
Henri Temerson, M.D., 45 West 90th Street, New York City, New York
Ralph A. Warwick, M.D., 3300 Federal Street, Camden, New Jersey
Donald Weisman, M.D., One Greenridge Avenue, White Plains, New York
Albert B. Weisz, M.D., 42 St. Nicholas Avenue, Brooklyn, New York
Lucy M. White, M.D., 245 Alexander Street, Rochester, New York
Armine Taylor Wilson, M.D., Alfred I. duPont Institute, Wilmington, Delaware
Lee Winston, M.D., 1321 S. Sixth Street, Philadelphia, Pennsylvania
Alfred Yankauer, Jr., M.D., 33 Riverside Drive, New York City, New York
Hedwig Zweig, M.D., 167 East 82nd Street, New York City, New York

EDITORIAL

THE first step of the Committee for Improvement of Child Health has been a big one. The Committee has drawn up a recommendation for federal support of pediatric education.*

This recommendation arises directly out of the Academy's nation-wide two-year Study of Child Health Services and is the first specific action taken by the ICH Committee. It is a step which has not been undertaken lightly. The proposal was drawn up after consideration in two meetings and consultation with deans of medical schools and heads of pediatric departments, officials of the Federal Security Administration and others particularly concerned. The recommendation was then submitted to the Executive Board and received the unanimous approval of the Board at a special meeting in Chicago on February 8, 1948.

The Academy's proposal attempts to put first things first. Efforts to strengthen pediatric education demand first priority if health services for children are to be improved, for without well trained physicians attempts to increase or improve child health are futile.

The Federal Security Administration is now pressing increasingly for federal support of medical education. It was therefore agreed that no time should be lost if the Academy wished to lead a move in support of pediatric education rather than finding itself in the conventional position of arguing for or against recommendations already formulated in government circles.

Much thought has been placed upon the advisability of advancing a recommendation in support of one branch of medical education when the financial crisis facing all medical education presents a far more serious and difficult problem. A limited categorical approach has certain specific points in its favor: (1) a recommendation for support of one part of the need may be received favorably as an experimental step toward meeting the larger need which will require a larger appropriation; (2) the Academy of Pediatrics has a large body of documentary evidence establishing the need; (3) large amounts of government money are now being spent specifically in programs for child health services which are often limited in their effectiveness by lack of well-trained physicians; (4) the cause of children and child health always has popular appeal.

In making this recommendation the Academy is undertaking a serious responsibility which may have far reaching effect. The statement as approved by the Executive Board appears in the Academy Division; it deserves the serious attention of all members of the Academy and others concerned in the teaching of pediatrics and the improvement of child health.

JOHN P. HUBBARD, M.D.

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* See Special Committee Reports in Academy Proceedings and Reports Division.